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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **33,359-01P**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **09/508913**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US98/19145	**SEPTEMBER 15, 1998**	**SEPTEMBER 19, 1997**

TITLE OF INVENTION

ATTENUATED RESPIRATORY SYNCYTIAL VIRUSES

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information: Sequence Listing Diskette&Rule 1.821(f) Statement Declaration of Alan M. Gordon re Deposits

CERTIFICATION UNDER 37 C.F.R. 1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL251674792US addressed to the Assistant Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.

March 16, 2000
Date

Alan M. Gordon
Alan M. Gordon

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U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/508913	PCT/US98/19145	33,359-01P

21. The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$840.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**	
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Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	11 - 20 =	0	x $18.00	**$0.00**
Independent claims	8 - 3 =	5	x $78.00	**$390.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
TOTAL OF ABOVE CALCULATIONS			=	**$1,230.00**
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Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**
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NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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March 16, 2000
DATE

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09/508913

ATTENUATED RESPIRATORY SYNCYTIAL VIRUSES

Field Of The Invention

This invention relates to respiratory syncytial viruses of subgroup B having at least one attenuating mutation in the RNA polymerase gene. This invention was made with Government support under a grant awarded by the Public Health Service. The Government has certain rights in the invention.

Background Of The Invention

Respiratory syncytial virus (RSV) is a nonsegmented, negative-sense, single stranded enveloped RNA virus. RSV belongs to the Family Paramyxoviridae, the Subfamily Pneumovirinae and the genus *Pneumovirus*. Pneumoviruses have 10 protein-encoding cistrons. These proteins in RSV are the nucleocapsid protein N, the phosphoprotein P, the nonglycosylated virion matrix protein M, the attachment protein G, the fusion protein F, the polymerase protein L, the nonstructural proteins NS1 and NS2, the small hydrophobic protein SH, and the transcription elongation factor protein M2.

The genomic RNA of RSV serves two template functions in the context of a nucleocapsid: as a template for the synthesis of messenger RNAs (mRNAs) and as a template for the synthesis of the antigenome (+) strand. RSV encodes and packages its own RNA dependent RNA Polymerase. Messenger RNAs are only synthesized once the virus has been uncoated in the infected cell. Viral replication occurs after synthesis of the mRNAs and requires the continuous synthesis of viral proteins. The newly synthesized antigenome (+) strand serves as the template for

generating further copies of the (-) strand genomic RNA.

The polymerase complex actuates and achieves transcription and replication by engaging the cis-acting signals at the 3' end of the genome, in particular, the promoter region. Viral genes are then transcribed from the genome template unidirectionally from its 3' to its 5' end. There is always less mRNA made from the downstream genes (e.g., the polymerase gene (L)) relative to their upstream neighbors (i.e., the nucleoprotein gene (N)). Therefore, there is always a gradient of mRNA abundance according to the position of the genes relative to the 3'-end of the genome.

RSV is the leading cause of viral pneumonia and bronchiolitis in infants and young children and is responsible for an estimated 95,000 hospitalizations and 4,500 deaths per year in the United States (Bibliography entries 1,2,3). Serious disease is most prevalent in infants 6 weeks to 6 months of age and in children with certain underlying illnesses (e.g. immunodeficiencies, congenital heart disease and bronchopulmonary dysplasia).

Two major subgroups of RSV have been identified, A and B, as well as antigenic variants within each subgroup (4). Multiple variants of each subgroup have been found to cocirculate in epidemics which occur annually during late fall, winter, and spring months (5). Most children are infected by two years of age. Complete immunity to RSV, however, does not develop and reinfections occur throughout life (6,7). These reinfections often are symptomatic, though generally confined to mild upper respiratory tract disease. A decrease in severity of disease is associated with two or more prior infections and, in some studies, with high levels of serum antibody,

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suggesting that protective immunity to RSV disease will accumulate following repeated infections (2,6,8,9,10,11). There is also evidence that children infected with one of the two major RSV subgroups may be somewhat protected against reinfection with the homologous subgroup (12). These observations suggest that it is both possible and worthwhile to develop an RSV vaccination regimen for infants and young children which would provide sufficient temporary immunity to protect against severe disease and death.

The identification of the two major subgroups of RSV has been based on reactivities of the F and G surface glycoproteins with monoclonal antibodies (4,13) and further delineated by sequence analysis (14,15). Both F and G proteins elicit neutralizing antibodies and immunization with these proteins provides protection against reinfection in mouse and cotton rat models (16,17,18). Most neutralizing antibodies are directed against the F protein. Beeler and Coelingh reported that out of 16 neutralization epitopes mapped to the F protein, 8 epitopes were conserved in all or all but one of 23 virus isolates tested (19). A high degree of sequence homology exists between the F protein of subgroups A and B (approximately 90% amino acid and approximately 80% nucleotide) whereas a much lower degree of homology exists between the G proteins (approximately 50-60% amino acid and approximately 60-70% nucleotide) (14). Correspondingly, immunity elicited by the F protein is more crossprotective between subgroups than is immunity elicited by the G protein (16,17). In mice, humoral immunity induced by both the F and G proteins is thought to be responsible for protection against reinfection with virus (20) whereas the CTL response is thought to be more important in resolution of primary infections

(21,22,23). The M2 (or 22K) protein has been shown to be a potent inducer of cytotoxic lymphocytes (CTL) in mice, with lesser CTL recognition of F, N, and P proteins (24,25). Human CTL's have been shown to recognize the F, M2, N, M, SH, and NS2 (or 1b) proteins (26). These data suggest that the F protein of either virus subgroup is a crucial immunogen in any RSV vaccine and that the G, M2, N, M, SH, and NS2 proteins should also be considered potential vaccine components.

For RSV, no vaccines of any kind are currently available. Thus, there is a need to develop vaccines against this human pathogen. Such vaccines would have to elicit an immune response in the recipient which will prevent serious RSV disease, i.e., LRD. The qualitative and quantitative features of such a favorable response are extrapolated from those seen in survivors of natural virus infection, who, though not protected from reinfection by the same or highly related viruses, are protected from serious or fatal disease.

A variety of approaches can be considered in seeking to develop such vaccines, including the use of: (1) purified individual viral protein vaccines (subunit vaccines); (2) inactivated whole virus preparations; and (3) live, attenuated viruses.

Subunit vaccines have the desirable feature of being pure, definable and relatively easily produced in abundance by various means, including recombinant DNA expression methods. To date, with the notable exception of hepatitis B surface antigen, viral subunit vaccines have generally only elicited short-lived and/or inadequate immunity, particularly in naive recipients.

Formalin inactivated whole virus preparations of polio (IPV) and hepatitis A have proven safe and

efficacious. In contrast, immunization with similarly inactivated whole RSV elicited unfavorable immune responses and/or response profiles which predisposed vaccinees to exaggerated or aberrant disease when subsequently confronted with the natural or "wild-type" virus.

Early attempts (1966) to vaccinate young children used a parenterally administered formalin-inactivated RSV vaccine. Unfortunately, several field trials of this vaccine revealed serious adverse reactions - the development of a severe illness with unusual features following subsequent natural infection with RSV (27,28). It has been suggested that this exposure to formalinized RSV antigen elicited an abnormal or unbalanced immune response profile, predisposing the vaccinee to RSV disease potentiation (29,30).

Several different live, attenuated viruses have proven remarkably effective as a means of achieving immunoprophylaxis. Pursuit of such vaccine candidates for RSV has been intense and long-standing.

RSV temperature sensitive (*ts*) mutants derived by chemical mutagenesis (31) were shown to be attenuated in rodent and non-human primate models (32,33).

Cold adaptation, a process by which virus is adapted to growth at temperatures colder than those at which it normally optimally grows, has been used to develop attenuated *ts* virus mutants for use as vaccines (for review see (34)). This method generally results in the accumulation of multiple genetic lesions which may help to confer phenotypic stability by reducing the probability that reversion of any one lesion will result in reversion of the relevant phenotype. Maassab has used stepwise cold adaptation to successfully

develop several *ts* influenza vaccine candidates currently in clinical trials (35,36,37). These mutants, which bear attenuating mutations in at least four different genes, appear to be attenuated, immunogenic, and phenotypically stable.

Belshe and co-workers have used cold adaptation to develop attenuated, *ts* strains of a paramyxovirus, parainfluenza virus type 3 (38,39). In this case, cold adaptation was carried out in primary African green monkey kidney cells by reducing temperatures to 20°C. Analysis of several virus variants cloned from this cold adapted population demonstrated that the level of attenuation and temperature sensitivity increased as the length of cold adaptation increased. These variants were shown to have reduced potential for virulence in humans, however the temperature sensitive phenotype was somewhat unstable in clinical trials (40).

RSV was successfully cold adapted to 25-26°C in several laboratories in the mid 1960's, but was found to be under-attenuated in vaccine trials (34,41,42). Maassab and DeBorde (34) have suggested this may be because cold adaptation was not carried out at low enough temperatures, or clones of adequately attenuated virus were not isolated from a genetically mixed population of cold-adapted virus.

Nevertheless, this means for generating attenuated live RSV vaccine candidates is lengthy and, at best, unpredictable, relying largely on the selective outgrowth of those randomly occurring genomic mutants with desirable attenuation characteristics. The resulting viruses may have the desired phenotype *in vitro*, and even appear to be attenuated in animal models. However, all too often they remain either under- or overattenuated in the human or animal host

for whom they are intended as vaccine candidates.

Thereafter, two live, attenuated RSV mutants were generated by cold passage or chemical mutagenesis. These RSV strains were found to have reduced virulence in seropositive adults. Unfortunately, they proved either over- or underattenuated when given to seronegative infants; in some cases they were also found to lack genetic stability (43,44). Another vaccination approach using parenteral administration of live virus was found ineffective and efforts along this line were discontinued (45). Notably, these live RSV vaccines were never associated with disease enhancement as observed with the formalin-inactivated RSV vaccine described above.

Currently, there are no RSV vaccines approved for administration to humans, although clinical trials are now in progress with cold-passaged, chemically mutagenized strains of RSV designated A2 and B-1.

Appropriately attenuated live derivatives of wild-type viruses offer a distinct advantage as vaccine candidates. As live, replicating agents, they initiate infection in recipients during which viral gene products are expressed, processed and presented in the context of the vaccinee's specific MHC class I and II molecules, eliciting humoral and cell-mediated immune responses, as well as the coordinate cytokine patterns, which parallel the protective immune profile of survivors of natural infection.

This favorable immune response pattern is contrasted with the delimited responses elicited by inactivated or subunit vaccines, which typically are largely restricted to the humoral immune surveillance arm. Further, the immune response profile elicited by some formalin inactivated whole virus vaccines, e.g., measles and respiratory syncytial virus vaccines

developed in the 1960's, have not only failed to provide sustained protection, but in fact have led to a predisposition to aberrant, exaggerated, and even fatal illness, when the vaccine recipient later confronted the wild-type virus.

While live, attenuated viruses have highly desirable characteristics as vaccine candidates, they have proven to be difficult to develop. The crux of the difficulty lies in the need to isolate a derivative of the wild-type virus which has lost its disease-producing potential (i.e., virulence), while retaining sufficient replication competence to infect the recipient and elicit the desired immune response profile in adequate abundance.

Historically, this delicate balance between virulence and attenuation has been achieved by serial passage of a wild-type viral isolate through different host tissues or cells under varying growth conditions (such as temperature). This process presumably favors the growth of viral variants (mutants), some of which have the favorable characteristic of attenuation. Occasionally, further attenuation is achieved through chemical mutagenesis as well.

This propagation/passage scheme typically leads to the emergence of virus derivatives which are temperature sensitive, cold-adapted and/or altered in their host range -- one or all of which are changes from the wild-type, disease-causing viruses -- i.e., changes that are associated with attenuation.

Rational vaccine design would be assisted by a better understanding of RSV, in particular, by the identification of the virally encoded determinants of virulence as well as those genomic changes which are responsible for attenuation.

Summary Of The Invention

Accordingly, it is an object of this invention to identify those regions of the polymerase gene of RSV subgroup B where mutations result in attenuation of those viruses.

It is a further object of this invention to produce recombinantly-generated RSV subgroup B which incorporate such attenuating mutations in their genomes.

It is still a further object of this invention to formulate vaccines containing such attenuated viruses.

These and other objects of the invention as discussed below are achieved by the generation and isolation of recombinantly-generated, attenuated, RSV subgroup B having at least one attenuating mutation in the RNA polymerase gene.

The at least one attenuating mutation in the RNA polymerase gene is selected from the group consisting of nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid).

In another embodiment of this invention, attenuated virus is used to prepare vaccines which elicit a protective immune response against the wild-type form of the virus.

In yet another embodiment of this invention, an isolated, positive strand, antigenomic message sense nucleic acid molecule (or an isolated, negative strand genomic sense nucleic acid molecule) having the

complete viral nucleotide sequence (whether of wild-type virus or virus attenuated by non-recombinant means) is manipulated by introducing one or more of the attenuating mutations described in this application to generate an isolated, recombinantly-generated attenuated virus. This virus is then used to prepare vaccines which elicit a protective immune response against the wild-type form of the virus.

In still another embodiment of this invention, such a complete wild-type or vaccine viral nucleotide sequence (as well as a revertant sequence) is used: (1) to design PCR primers for use in a PCR assay to detect the presence of the corresponding virus in a sample; or (2) to design and select peptides for use in an ELISA to detect the presence of the corresponding virus in a sample.

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Brief Description Of The Figures

Figure 1 shows a flow chart detailing the propagation of RSV 2B working seed MK7V14b and RSV 3A working seed MK8V17b.

Figure 2 shows growth and cytopathic effect of RSV 2B at temperatures from 26oC to 36°C in Vero cells.

Figure 3 shows growth and cytopathic effect of RSV 3A at temperatures from 26°C to 36°C in Vero cells.

Figure 4 graphically shows titration results obtained at each passage of RSV 2B and RSV 3A.

Figure 5 shows the growth curves of RSV 2B, RSV 2Bp24G, RSV 2Bp20L, RSV 3A, RSV 3Ap20E and RSV 3Ap20F in Vero cells at temperatures from 20°C to 40°C.

Figure 6 compares graphically the growth of

RSV 2B and RSV 2Bp20L in cotton rats from 3 to 7 days post-infection.

Figure 7 compares the relative growth and pathogenicity of RSV 2B and RSV 2Bp20L in four (4) year old seropositive chimps.

Figure 8 is a diagram showing virus titrations for monkeys infected with the RSV 2B *ts* mutants and subsequently challenged with the parental strain.

Figure 9 is a diagram showing virus growth in African green monkey cells infected with the RSV 3A *ts* mutants and challenged with the parental 3A strain.

Figure 10 is a diagram showing a growth study in African green monkeys comparing TS-1 with RSV 2Bp33F and 3Ap28F.

Figure 11 depicts a genetic map of the RSV subgroup B wild-type strains designated 2B and 18537 (top portion), the intergenic sequences of those strains (middle portion) and the 68 nucleotide overlap between the M2 and L genes (bottom portion). The RSV 2B stain has six fewer nucleotides in the G gene, encoding two fewer amino acid residues in the G protein, as compared to the 18537 strain. The 2B strain has 145 nucleotides in the 5' trailer region, as compared to 149 nucleotides in the 18537 strain. The 2B strain has one more nucleotide in each of the NS-1, NS-2 and N genes, and one fewer nucleotide in each of the M and F genes, as compared to the 18537 strain.

Detailed Description Of The Invention

The first step in the identification of attenuating mutations in the L gene of RSV subgroup B vaccine strains was the generation of those strains from wild-type strains. The original RSV subgroup B

vaccine strains (as well as subgroup A vaccine strains) were generated by cold adaptation of the wild-type virus. Cold adaptation comprises obtaining live virulent virus derived from clinical isolates that have been isolated in primary rhesus monkey kidney cells. These are then passed in Vero cells at 35-36°C and plaque purified. Preferably, the Vero cells are passage 133 to 148 of the Vero cell line CCL81, obtained from the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland, U.S.A. 20852. The maintenance medium is preferably MEM with 2% FBS, L-glutamine, non-essential amino acids and 20mM Hepes pH 7.5, and the freezing medium is MEM with 10% FBS and 20mM Hepes pH 7.5.

A confluent monolayer of Vero cells is inoculated with about 1.0 ml of virus inoculum, and virus is allowed to absorb for about one to two hours (preferably, 70 to 120 minutes, and most preferably 90 minutes) at ambient temperature (about 18°C to about 25°C).

The virus flask is incubated at about 18°C to about 26°C, preferably about 20°C, for about two to fifteen days. Virus is harvested by removing the medium and replacing it with freezing medium. The flask is then frozen directly at -70°C, then thawed in a 32°C water bath.

A portion (about 1 ml) is removed from the freeze-thaw lysate and is used to inoculate Vero cells; the process is then repeated. The remaining freeze-thaw lysate is stored at -70°C. It can be used to perform virus titrations and plaque purify virus.

To plaque purify virus, the freeze-thaw lysate is thawed in a 32°C water bath. About three to five serial dilutions of the lysate are made in the maintenance medium. Six-well, twenty-four well, or

ninety-six well plates containing confluent Vero cells are rinsed with a phosphate buffered saline solution. Wells are inoculated with virus dilution, using only enough volume to cover the bottom of the well. Virus inoculum is adsorbed for 90 minutes at ambient temperature. Wells are overlaid with 1% methylcellulose in MEM-maintenance medium. Plates are incubated at 32°C for five days. Isolated plaques are identified microscopically by looking for typical syncytial plaques, and wells are marked. Plaques are picked at marked sites using small bore pipette or pipette tip and are emulsified in 0.5 ml maintenance medium for 1-3 hours at 4°C. Picked plaques are used to inoculate duplicates of 25 cm^2 flask or 96-well plates containing Vero cell monolayers as described above. Duplicate inoculated flasks or plates are overlaid with maintenance medium. One duplicate is incubated at 32°C and the other at 39°C for 5-10 days. Flasks or plates incubated at 32°C are examined microscopically for virus cytopathic effect (CPE). Flasks or plates incubated at 39°C are stained by immunoperoxidase assay for RSV specific antigen. Flasks or plates which demonstrate easily detectable CPE at 32°C and little or no detectable RSV antigen by immunoperoxidase staining are selected as containing temperature sensitive (*ts*) mutants. Virus from the selected flask or plate described above are harvested by freeze-thaw technique. This virus represents a plaque purified mutant.

Cold adaptation as just described was used to develop attenuated strains of RSV from two parental strains derived from clinical isolates. Seven *ts* mutants were isolated, four from a subgroup B virus (RSV 2B) and three from a subgroup A virus (RSV 3A). All seven mutants displayed a temperature sensitive

phenotype in Vero cell culture, each with unique characteristics. All mutants were attenuated in growth in cotton rats, but displayed different phenotypes. Growth of one of the *ts* mutants, RSV 2Bp20L, was shown to be attenuated in seropositive chimpanzees. All seven mutants retained two major neutralization epitopes.

Cold adaptation of RSV had previously been done in primary or diploid cell lines (bovine embryonic kidney, WI38, and cercopithecus monkey kidney) at temperatures beginning at 34°C-37°C and decreasing to 25°C-26°C. No attempt had been made to isolate multiple individual mutant phenotypes from the cold-adapted virus (37,46,47).

The approach described herein to cold-adapting RSV differed in several significant ways from these previous attempts. This procedure started with a subgroup A and subgroup B virus of different strains than those used previously. These strains bore distinct phenotypic differences from the reference strains and each other. These strains were passed several times to adapt virus to Vero cells and to plaque purify virus. Virus was passaged in a continuous cell line, Vero cells, rather than a diploid or primary cell line. Several strategies of temperature change were used, to provide a greater potential for isolation of a variety of mutant phenotypes.

Unlike previous RSV cold adaptation strategies where cold adaptation had started at 34-37°C and gone down to 25-26°C, cold adaptation started at either 26°C (since it was found that the parental strains grew well at this temperature) or 22°C, and gradually reduced the growth temperature to 20°C. Passage strategies attempted to cover both the

recommendation of "slow" adaptation to very low temperatures as proposed by Massab and DeBorde (37), as well as efforts to try a faster and more aggressive approach. RNA viruses mutate at such a high frequency that any population of virus will contain a number of individual virus variants (48). Therefore, a variety of virus mutants were isolated from individual flasks at various virus passage levels and from different cold adaptation strategies.

The results were interesting and somewhat unexpected. The rate at which virus became adapted (i.e., grew to consistently high titers at the 20°C temperature), was most affected by the strain of virus used, implying a significant host-related factor in adaptation. RSV 2B easily adapted to the cold temperatures, even using a rapid adaptation scheme. In contrast, RSV 3A grew poorly at the low temperatures. RSV 3A was eventually cold-adapted using the slow passage scheme, but the more rapid adaptation approaches did not appear promising and were discontinued. Based on cold adaptation experiences reported by other researchers, it was expected *ts* mutants would arise and eventually become the predominant virus variants in the cold-adapted populations. For example, Belshe and Hissom (41) reported that with parainfluenza virus type 3 adapted to grow at 20°C, 80% of plaque purified virus clones were *ts* by passage 18 and 100% were *ts* by passage 45. In this study, even after 38-40 low temperature passages, including up to 32 passages done at 20°C, RSV *ts* mutants remained a minor population. This would suggest that *ts* and cold-adapted phenotypes may not be as strongly linked in RSV as they are in other viruses.

The level of attenuation is a critical factor in developing vaccines for any target population and is

of particular importance for vaccines intended for infants and young children. Virus must be sufficiently attenuated to not cause disease, yet grow well enough in the vaccine to elicit protective immunity.

Widely accepted markers for attenuation are *ts* phenotype and reduced growth in animal models. However, these markers are only approximate and testing must eventually be done in the target population. The RSV 3A *ts* mutants could be distinguished from the RSV 3A parental virus by reduced replication in both the nose and lungs. Also of note, although the RSV 3A parental virus grew much better in the nose than the lungs of cotton rats, virus recovery was similar in both nose and lungs of BALB/c mice. These data suggest that the attenuation seen in cotton rats is due to more than one factor, and that this factor is not directly related to temperature sensitivity as measured *in vitro*. The cotton rat is relatively nonpermissive for growth of RSV and disease does not develop, suggesting that this model is an unreliable indicator of level of attenuation in humans.

In contrast, chimpanzees are highly susceptible to RSV infection and develop an upper and lower respiratory tract disease that is very similar to that seen in humans. In seropositive chimps, it was found that the RSV 2B parental strain caused mild upper respiratory tract disease similar to that caused by natural RSV infections in adult humans. The RSV 2Bp20L mutant did not grow, clearly demonstrating that this *ts* mutant was attenuated in a permissive host as well as the non-permissive cotton rat. The level of attenuation is best assessed in a seronegative chimp, as prior virus exposure will affect the host response to virus challenge. Unfortunately, testing in seronegative chimps is severely hampered by the limited

availability of these animals.

The mutants described herein bear the desirable traits of an attenuated, phenotypically stable, and immunogenic RSV vaccine virus in the human target population.

The immunopotency of the recombinantly-generated RSV subgroup B vaccine is determined by monitoring the immune response of test animals following immunization with the vaccine. Test animals include, but are not limited to, mice, rats (e.g., cotton rats), rabbits, primates, e.g., African green monkeys, chimps, and human subjects. Methods of introduction of the immunogen may include oral, parenteral, topical, intranasal or any other standard routes of immunizations. The immune response of the test subjects is analyzed by four approaches: (a) the reactivity of the resultant immune serum to authentic RSV antigens, as assayed by known techniques, e.g., enzyme linked immunosorbant assay (ELISA), immunoblots, radioimmunoprecipitations, etc.; (b) the ability of the immune serum to neutralize RSV infectivity *in vitro*; (c) the ability of the immune serum to inhibit virus fusion *in vitro*; and (d) protection from RSV infection or significant disease.

The cold-adapted RSV mutants are capable of eliciting an immune response when administered to a subject without causing significant disease, such as respiratory distress or otitis media. As used herein, the term "cold-adapted mutant" means an attenuated virus that has been attenuated by propagation at lower than optimal temperatures. Examples of cold-adapted mutant viruses have been provided as described above. The cold-adapted mutant RSV may be a mutant of subgroup A, such as the group consisting of 3Ap20E, 3Ap20F and 3Ap28F. The cold-adapted mutant RSV may also be a

mutant of the subgroup B, such as the group consisting of 2Bp33F, 2Bp24G, 2Bp20L and 2Bp34L. The subgroup B viruses are then sequenced and differences between wild-type and mutant strains are identified. Those mutations which contribute to the attenuated phenotype are then assessed.

Transcription and replication of negative-sense, single stranded RNA viral genomes such as RSV subgroup B are achieved through the enzymatic activity of a multimeric protein acting on the ribonucleoprotein core (nucleocapsid). Naked genomic RNA cannot serve as a template. Instead, these genomic sequences are recognized only when they are entirely encapsidated by the N protein into the nucleocapsid structure. It is only in that context that the genomic and antigenomic terminal promoter sequences are recognized to initiate the transcriptional or replication pathways.

All paramyxoviruses require the two viral proteins, L and P, for these polymerase pathways to proceed. The pneumoviruses, including RSV, also require the transcription elongation factor M2 for the transcriptional pathway to proceed efficiently. Additional cofactors may also play a role, including perhaps the virus-encoded NS1 and NS2 proteins, as well as perhaps host-cell encoded proteins.

However, considerable evidence indicates that it is the L protein which performs most if not all the enzymatic processes associated with transcription and replication, including initiation, and termination of ribonucleotide polymerization, capping and polyadenylation of mRNA transcripts, methylation and perhaps specific phosphorylation of P proteins. The L protein's central role in genomic transcription and replication is supported by its large size, sensitivity to mutations, and its catalytic level of abundance in

the transcriptionally active viral complex (49).

These considerations led to the proposal that L proteins consist of a linear array of domains whose concatenated structure integrates discrete functions (50). Indeed, three such delimited, discrete elements within the negative-sense virus L protein have been identified based on their relatedness to defined functional domains of other well-characterized proteins. These include: (1) a putative RNA template recognition and/or phosphodiester bond formation domain; (2) an RNA binding element; and (3) an ATP binding domain. All prior studies of L proteins of nonsegmented negative-sense, single stranded RNA viruses have revealed these putative functional elements (50).

In summary, the invention comprises the identification of changes in the polymerase gene (L) which result in attenuation of the virus while retaining sufficient ability of the virus to replicate. Attenuation is optimized by rational mutations of the polymerase gene, which provide the desired balance of replication efficiency: so that the virus vaccine is no longer able to produce disease, yet retains its capacity to infect the vaccinee's cells, to express sufficiently abundant gene products to elicit the full spectrum and profile of desirable immune responses, and to reproduce and disseminate sufficiently to maximize the abundance of the immune response elicited.

Animal studies have demonstrated a decrease in viral replication sufficient to avoid illness but adequate to elicit the desired immune response. This likely represents a decrease in transcription, a decrease in gene expression of virally encoded proteins, a decrease in antisense templates and, therefore, the production of fewer new genomes. The

resulting attenuated viruses are significantly less virulent than the wild-type.

The attenuating mutations described herein may be introduced into viral strains by two methods:

(1) Conventional means such as chemical mutagenesis during virus growth in cell cultures to which a chemical mutagen has been added, selection of virus that has been subjected to passage at suboptimal temperature in order to select temperature sensitive and/or cold-adapted mutations, identification of mutant virus that produce small plaques in cell culture, and passage through heterologous hosts to select for host range mutations. These viruses are then screened for attenuation of their biological activity in an animal model. Attenuated viruses are subjected to nucleotide sequencing of their polymerase genes to locate the sites of attenuating mutations. Once this has been done, method (2) is then carried out.

(2) A preferred means of introducing attenuating mutations comprises making predetermined mutations using site-directed mutagenesis. These mutations are identified either by method (1) or by reference to closely-related viruses whose attenuating mutations are already known. One or more mutations are introduced into the polymerase gene. Cumulative effects of different combinations of coding and non-coding changes can also be assessed.

The mutations to the polymerase gene are introduced by standard recombinant DNA methods into a DNA copy of the viral genome. This may be a wild-type or a modified viral genome background (such as viruses modified by method (1)), thereby generating a new virus. Infectious clones or particles containing these attenuating mutations are generated using the cDNA "rescue" system, which has been applied to a variety of

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viruses, including Sendai virus (51); measles virus (52); respiratory syncytial virus (53); rabies (54); vesicular stomatitis virus (VSV) (55); and rinderpest virus (56); these references are hereby incorporated by reference. See, for RSV rescue, published International patent application WO 97/12032, designating the United States (57); this application is hereby incorporated by reference.

Briefly, all Mononegavirales rescue systems can be summarized as follows: Each requires a cloned DNA equivalent of the entire viral genome placed between a suitable DNA-dependent RNA polymerase promoter (e.g., the T7 RNA polymerase promoter) and a self-cleaving ribozyme sequence (e.g., the hepatitis delta ribozyme) which is inserted into a propagatable bacterial plasmid. This transcription vector provides the readily manipulable DNA template from which the RNA polymerase (e.g., T7 RNA polymerase) can faithfully transcribe a single-stranded RNA copy of the viral antigenome (or genome) with the precise, or nearly precise, 5' and 3' termini. The orientation of the viral genomic DNA copy and the flanking promoter and ribozyme sequences determine whether antigenome or genome RNA equivalents are transcribed. Also required for rescue of new virus progeny are the virus-specific trans-acting proteins needed to encapsidate the naked, single-stranded viral antigenome or genome RNA transcripts into functional nucleocapsid templates: the viral nucleocapsid (N or NP) protein, the polymerase-associated phosphoprotein (P) and the polymerase (L) protein. These proteins comprise the active viral RNA-dependent RNA polymerase which must engage this nucleocapsid template to achieve transcription and replication.

The trans-acting proteins required for RSV

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rescue are the encapsidating protein N, the polymerase complex proteins, P and L, and an additional protein, M2, the RSV-encoded transcription elongation factor.

Typically, these viral trans-acting proteins are generated from one or more plasmid expression vectors encoding the required proteins, although some or all of the required trans-acting proteins may be produced within mammalian cells engineered to contain and express these virus-specific genes and gene products as stable transformants.

The typical (although not necessarily exclusive) circumstances for rescue include an appropriate mammallian cell milieu in which T7 polymerase is present to drive transcription of the antigenomic (or genomic) single-stranded RNA from the viral genomic cDNA-containing transcription vector. Either cotranscriptionally or shortly thereafter, this viral antigenome (or genome) RNA transcript is encapsidated into functional templates by the nucleocapsid protein and engaged by the required polymerase components produced concurrently from co-transfected expression plasmids encoding the required virus-specific trans-acting proteins. These events and processes lead to the prerequisite transcription of viral mRNAs, the replication and amplification of new genomes and, thereby, the production of novel viral progeny, i.e., rescue.

For the rescue of rabies, VSV and Sendai, T7 polymerase is provided by recombinant vaccinia virus VTF7-3. This system, however, requires that the rescued virus be separated from the vaccinia virus by physical or biochemical means or by repeated passaging in cells or tissues that are not a good host for poxvirus. For measles virus (MV) cDNA rescue, this requirement is avoided by creating a cell line that

expresses T7 polymerase, as well as viral N and P proteins. Rescue is achieved by transfecting the genome expression vector and the L gene expression vector into the helper cell line. Advantages of the host-range mutant of the vaccinia virus, MVA-T7, which expresses the T7 RNA polymerase, but does not replicate in mammalian cells, are exploited to rescue RSV, Rinderpest virus and MV. After simultaneous expression of the necessary encapsidating proteins, synthetic full length antigenomic viral RNA are encapsidated, replicated and transcribed by viral polymerase proteins and replicated genomes are packaged into infectious virions. In addition to such antigenomes, genome analogs have now been successfully rescued for Sendai and PIV-3 (58,59).

The rescue system thus provides a composition which comprises a transcription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of RSV subgroup B having at least one attenuating mutation in the RNA polymerase gene, together with at least one expression vector which comprises at least one isolated nucleic acid molecule encoding the trans-acting N, P, L and M2 proteins necessary for encapsidation, transcription and replication. Host cells are then transformed or transfected with the at least two vectors just described. The host cells are cultured under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated virus.

The rescued infectious RSV is then tested for its desired phenotype (temperature sensitivity, cold adaptation, plaque morphology, and transcription and replication attenuation), first by *in vitro* means.

If the attenuated phenotype of the rescued

virus is present, challenge experiments are conducted with an appropriate animal model. Non-human primates provide the preferred animal model for the pathogenesis of human disease. These primates are first immunized with the attenuated, recombinantly-generated virus, then challenged with the wild-type form of the virus. Monkeys are infected by various routes, including but not limited to intranasal or intratracheal routes of inoculation (60). Protection in non-human primates is measured by such criteria as disease signs and symptoms, virus shedding and antibody titers. If the desired criteria are met, the attenuated, recombinantly-generated virus is considered a viable vaccine candidate for testing in humans. The "rescued" virus is considered to be "recombinantly-generated", as are the progeny and later generations of the virus, which also incorporate the attenuating mutations.

Even if a "rescued" virus is underattenuated or overattenuated relative to optimum levels for vaccine use, this is information which is valuable for developing such optimum strains.

Optimally, a codon containing an attenuating point mutation may be stabilized by introducing a second or a second plus a third mutation in the codon without changing the amino acid encoded by the codon bearing only the attenuating point mutation. Infectious virus clones containing the attenuating and stabilizing mutations are also generated using the cDNA "rescue" system described above.

Two major subgroups of human RSV, designated A and B, have been identified based on reactivities of the F and G surface glycoproteins with monoclonal antibodies (4). More recently, the A and B lineages of RSV strains have been confirmed by sequence analysis (14,15). Bovine, ovine, and caprine strains of this

virus have also been isolated. The host specificity of the virus is most clearly associated with the G attachment protein, which is highly divergent between the human and the bovine/ovine strains (61,62), and may be influenced, at least in part, by receptor binding.

RSV is the primary cause of serious viral pneumonia and bronchiolitis in infants and young children. Serious disease, i.e., lower respiratory tract disease (LRD), is most prevalent in infants less than six months of age. It most commonly occurs in the nonimmune infant's first exposure to RSV. RSV additionally is associated with asthma and hyperreactive airways and it is a significant cause of mortality in "high risk" children with bronchopulmonary dysplasia and congenital heart disease (CHD). It is also one of the common viral respiratory infections predisposing to otitis media in children. In adults, RSV generally presents as uncomplicated upper respiratory illness; however, in the elderly it rivals influenza as a predisposing factor in the development of serious LRD, particularly bacterial bronchitis and pneumonia. Disease is always confined to the respiratory tract, except in the severely immunocompromised, where dissemination to other organs can occur. Virus is spread to others by fomites contaminated with virus-containing respiratory secretions, and infection initiates through the nasal, oral, or conjunctival mucosa.

RSV disease is seasonal and virus is usually isolated only in the winter months, e.g., from November to April in northern latitudes. The virus is ubiquitous, and over 90% of children have been infected at least once by 2 years of age. Multiple strains cocirculate. There is no direct evidence of antigenic drift (such as that seen with influenza A viruses), but

sequence studies demonstrating accumulation of amino acid changes in the hypervariable regions of the G protein and SH proteins suggest that immune pressure may drive virus evolution.

In mouse and cotton rat models, both the F and G proteins of RSV elicit neutralizing antibodies and immunization with these proteins alone provides longterm protection against reinfection (16,17).

In humans, complete immunity to RSV does not develop and reinfections occur throughout life (6,7); however, there is evidence that immune factors will protect against severe disease. A decrease in severity of disease is associated with two or more prior infections and there is evidence that children infected with one of the two major RSV subgroups may be somewhat protected against reinfection with the homologous subgroup (13), observations which suggest that a live attenuated virus vaccine may provide protection sufficient to prevent serious morbidity and mortality. Infection with RSV elicits both antibody and cell mediated immunity. Serum neutralizing antibody to the F and G proteins has been associated, in some studies, with protection from LRD, although reduction in upper respiratory disease (URD) has not been demonstrated. High levels of serum antibody in infants is associated with protection against LRD, and adminstration of intravenous immunoglobulin with high RSV neutralizing antibody titers has been shown to protect against severe disease in high risk children (7,10,63). The role of local immunity, and nasal antibody in particular, is being investigated.

The RSV virion consists of a ribonucleoprotein core contained within a lipoprotein envelope. The virions of pneumoviruses are similar in size and shape to those of all other paramyxoviruses.

When visualized by negative staining and electron microscopy, virions are irregular in shape and range in diameter from 150-300 nm (64). The nucleocapsid of this virus is a symmetrical helix similar to that of other paramyxoviruses, except that the helical diameter is 12-15 nm rather than 18nm. The envelope consists of a lipid bilayer that is derived from the host membrane and contains virally coded transmembrane surface glycoproteins. The viral glycoproteins mediate attachment and penetration and are organized separately into virion spikes. All members of paramyxovirus subfamily have hemagglutinating activity, but this function is not a defining feature for pneumoviruses, being absent in RSV but present in PVM (65). Neuraminidase activity is present in members of the genera Paramyxovirus, Rubulavirus, and is absent in Morbillivirus and Pneumovirus of mice (PVM) (65).

RSV possesses two subgroups, designated A and B. The wild-type RSV (strain 2B) genome is a single strand of negative-sense RNA of 15,218 nucleotides (SEQ ID NO:1) that are transcribed into ten major subgenomic mRNAs. Each of the ten mRNAs encodes a major polypeptide chain: Three are transmembrane surface proteins (G, F and SH); three are the proteins associated with genomic RNA to form the viral nucleocapsid (N, P and L); two are nonstructural proteins (NS1 and NS2) which accumulate in the infected cells but are also present in the virion in trace amounts and may play a role in regulating transcription and replication; one is the nonglycosylated virion matrix protein (M); and the last is M2, another nonglycosylated protein recently shown to be an RSV-specified transcription elongation factor (see Figure 11). These ten viral proteins account for nearly all of the viral coding capacity.

The viral genome is encapsidated with the major nucleocapsid protein (N), and is associated with the phosphoprotein (P), and the large (L) polymerase protein. These three proteins have been shown to be necessary and sufficient for directing RNA replication of cDNA encoded RSV minigenomes (66). Further studies have shown that for transcription to proceed with full processing, the M2 protein (ORF 1) is required (64). When the M2 protein is missing, truncated transcripts predominate, and rescue of the full length genome does not occur (64).

Both the M (matrix protein) and the M2 proteins are internal virion-associated proteins that are not present in the nucleocapsid structure. By analogy with other nonsegmented negative-stranded RNA viruses, the M protein is thought to render the nucleocapsid transcriptionally inactive before packaging and to mediate its association with the viral envelope. The NS1 and NS2 proteins have only been detected in very small amounts in purified virions, and at this time are considered non-structural. Their functions are uncertain, though they may be regulators of transcription and replication. Three transmembrane surface glycoproteins are present in virions: G, F, and SH. G and F (fusion) are envelope glycoproteins that are known to mediate attachment and penetration of the virus into the host cell. In addition, these glycoproteins represent major independent immunogens (3). The function of the SH protein is unknown, although a recent report has implicated its involvement in the fusion function of the virus (67).

The genomes of two wild-type RSV subgroup B strains (2B and 18537) have now been sequenced in their entirety (see SEQ ID NOS:1 and 3, discussed below). Genomic RNA is neither capped nor polyadenylated (68).

In both the virion and intracellularly, genomic RNA is tightly associated with the N protein.

The 3' end of the genomic RNA consists of a 44-nucleotide extragenic leader region that is presumed to contain the major viral promoter (68; Fig. 11). The 3' genomic promoter region is followed by ten viral genes in the order 3'-NS1-NS2-N-P-M-SH-G-F-M2-L-5' (Fig. 11). The L gene is followed by a 145-149 nucleotide extragenic trailer region (see Figure 11). Each gene begins with a conserved nine-nucleotide gene start signal 3'-GGGGCAAAU (except for the ten-nucleotide gene start signal of the L gene, which is 3'-GGGACAAAAU; differences underlined). For each gene, transcription begins at the first nucleotide of the signal. Each gene terminates with a semi-conserved 12-14 nucleotide gene end (3'-A G U/G U/A ANNN U/A A_{3-5}) (where N can be any of the four bases) that directs transcription termination and polyadenylation (Fig. 11). The first nine genes are non-overlapping and are separated by intergenic regions that range in size from 3 to 56 nucleotides for RSV B strains (Fig. 11). The intergenic regions do not contain any conserved motifs or any obvious features of secondary structure and have been shown to have no influence on the preceding and succeeding gene expression in a minreplicon system (Fig. 11). The last two RSV genes overlap by 68 nucleotides (Fig. 11). The gene-start signal of the L gene is located inside of, rather than after, the M2 gene. This 68 nucleotide overlap sequence encodes the last 68 nucleotides of the M2 mRNA (exclusive of the Poly-A tail), as well as the first 68 nucleotides of the L mRNA.

Ten different species of subgenomic polyadenylated mRNAs and a number of polycistronic polyadenylated read-through transcripts are the

products of genomic transcription (64). Transcriptional mapping studies using UV light mediated genomic inactivation showed that RSV genes are transcribed in their 3' to 5' order from a single promoter near the 3' end (69). Thus, RSV synthesis appears to follow the single entry, sequential transcription model proposed for all Mononegavirales (70,71). According to this model, the polymerase (L) contacts genomic RNA in the nucleocapsid form at the 3' genomic promoter region and begins transcription at the first nucleotide. RSV mRNAs are co-linear copies of the genes, with no evidence of mRNA editing or splicing.

Sequence analysis of intracellular RSV mRNAs showed that synthesis of each transcript begins at the first nucleotide of the gene start signal (64). The 5' end of the mRNAs are capped with the structure m7G(5')ppp(5')Gp (where the underlined G is the first template nucleotide of the mRNA) and the mRNAs are polyadenylated at their 3' ends (72). Both of these modifications are thought to be made co-transcriptionally by the viral polymerase. Three regions of the RSV 3' genomic promoter have been found to be important as cis acting elements (73). These regions are the first ten nucleotides (presumably acting as a promoter), nucleotides 21-25, and the gene start signal located at nucleotides 45-53 (73). Unlike other Paramyxovirinae, such as measles, Sendai and PIV-3, the remainder of the leader and non-coding region of NS1 gene of RSV was found to be highly tolerant of insertions, deletions and substitutions (73).

Additionally, by saturation mutagenesis (wherein each base is replaced independently by each of the other three bases and compared for translation and replication efficiencies) within the first 12

nucleotides of the 3' genomic promoter region, a U-tract located at nucleotides 6-10 was shown to be highly inhibitory to substitutions (73). In contrast, the first five nucleotides were relatively tolerant of a number of substitutions and two of them at position four were up-regulatory mutations, resulting in a four- to 20-fold increase in RSV-CAT RNA replication and transcription. Using a bi-cistronic minireplicon system, gene-start and gene-end motifs were shown to be signals for mRNA synthesis and appear to be self contained and largely independent of the nature of adjoining sequence (74).

The L gene start signal lies 68 nucleotides upstream of the M2 gene-end signal, resulting in gene overlap (Fig. 11) (64). The presence of the M2 gene-end signal within the L gene results in a high frequency of premature termination of L gene transcripts. Full length L mRNA is much less abundant and is made when the polymerase fails to recognize the M2 gene-end motif. This results in much lower transcription of L mRNA. The gene overlap seems incompatible with a model of linear sequential transcription. It is not known whether the polymerase that exits the M2 gene jumps backward to the L gene-start signal or whether there is a second, internal promoter for L gene transcription (64). It is also possible that the L gene is accessible by a small fraction of polymerases that fail to start transcription at the M2 gene-start signal and slide down the M2 gene to the L gene-start signal.

The relative abundance of each RSV mRNA decreases with the distance of its gene from the promoter, presumably due to polymerase fall-off during sequential transcription (69). Gene overlap is a second mechanism that reduces the synthesis of full

length L mRNA. Also, certain mRNAs have features that might reduce the efficiency of translation. The initiation codon for SH mRNA is in a suboptimal Kozak sequence context, while the G ORF begins at the second methionyl codon in the mRNA.

RSV RNA replication is thought (64) to follow the model proposed from studies with vesicular stomatitis virus and Sendai virus (70,71). This involves a switch from the stop-start mode of mRNA synthesis to an antiterminator read-through mode. This results in synthesis of positive sense replication-intermediate (RI) RNA that is an exact complementary copy of genomic RNA. This serves in turn as the template for the synthesis of progeny genomes. The mechanism involved in the switch to the antiterminator mode is proposed to involve cotranscriptional encapsidation of the nascent RNA by N protein (70,71). RNA replication in RSV like other nonsegmented negative-strand RNA viruses is dependent on ongoing protein synthesis (75). Predicted RI RNA has been detected for the standard virus as well as RSV-CAT minigenome (64,75). RI RNA was 10-20 fold less abundant intracellularly than was the progeny genome both for the standard and the minigenome system. The nucleotide sequences (in positive strand, antigenomic, message sense) of various wild-type, vaccine and revertant RSV strains, as well as the deduced amino acid sequences of the RNA polymerase (L protein) of these RSV viruses, are set forth as follows with reference to the appropriate SEQ ID NOS. contained herein:

Virus	Nucleotide Sequence	L Protein Sequence
Wild-Type		
2B	SEQ ID NO:1	SEQ ID NO:2
18537	SEQ ID NO:3	SEQ ID NO:4
Vaccine		
2B33F	SEQ ID NO:5	SEQ ID NO:6
2B20L	SEQ ID NO:7	SEQ ID NO:8
Revertant		
2B33F TS(+)	SEQ ID NO:9	SEQ ID NO:10
2B20L TS(+)	SEQ ID NO:11	SEQ ID NO:12

It is noted that the Sequence Listings recite "DNA"; this is necessary for the antigenomic message sense RNA to be provided in full (reciting sequences as "RNA" causes each "T" to be deleted from the sequence).

Each RSV virus genome encodes an L protein that is 2,166 amino acids long. Genome length and other nucleotide information is as follows:

Virus Wild-Type	Genome Length	L Start Codon	L Stop Codon
2B	15218	8502-8504	15000-15002
18537	15229	8509-8511	15007-15009
Vaccine			
2B33F	15219	8503-8505	15001-15003
2B20L	15219	8503-8505	15001-15003
Revertant			
2B33F TS(+)	15219	8503-8505	15001-15003
2B20L TS(+)	15219	8503-8505	15001-15003

As detailed in Example 8 (especially Tables

21 and 22) below, the key potentially attenuating sites for the L protein of RSV subgroup B are as follows: amino acid residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid). It is understood that the nucleotide changes responsible for these amino acid changes are not limited to those set forth in Example 8 below; all changes in nucleotides which result in codons which are translated into these amino acids are within the scope of this invention.

The attenuated RSV subgroup B viruses of this invention exhibit a substantial reduction of virulence compared to wild-type viruses which infect human and animal hosts. The extent of attenuation is such that symptoms of infection will not arise in most immunized individuals, but the virus will retain sufficient replication competence to be infectious in and elicit the desired immune response profile in the vaccinee.

The attenuated RSV subgroup B viruses of this invention may be used to formulate a vaccine. To do so, the attenuated virus is adjusted to an appropriate concentration and formulated with any suitable vaccine adjuvant, diluent or carrier. Physiologically acceptable media may be used as carriers. These include, but are not limited to: an appropriate isotonic medium, phosphate buffered saline and the like. Suitable adjuvants include, but are not limited to MPL™ (3-O-deacylated monophosphoryl lipid A; RIBI ImmunoChem Research, Inc., Hamilton, MT) and IL-12 (Genetics Institute, Cambridge, MA).

In one embodiment of this invention, the formulation including the attenuated virus is intended for use as a vaccine. The attenuated virus may be mixed

with cryoprotective additives or stabilizers such as proteins (e.g., albumin, gelatin), sugars (e.g., sucrose, lactose, sorbitol), amino acids (e.g., sodium glutamate), saline, or other protective agents. This mixture is maintained in a liquid state, or is then dessicated or lyophilized for transport and storage and mixed with water immediately prior to administration.

Formulations comprising the attenuated viruses of this invention are useful to immunize a human or animal subject to induce protection against infection by the wild-type counterpart of the attenuated virus. Thus, this invention further provides a method of immunizing a subject to induce protection against infection by an RSV subgroup B virus by administering to the subject an effective immunizing amount of a vaccine formulation incorporating an attenuated version of that virus as described hereinabove.

A sufficient amount of the vaccine in an appropriate number of doses must be administered to the subject to elicit an immune response. Persons skilled in the art will readily be able to determine such amounts and dosages. Administration may be by any conventional effective form, such as intranasally, parenterally, orally, or topically applied to any mucosal surface such as intranasal, oral, eye, vaginal or rectal surface, such as by an aerosol spray. The preferred means of administration is by intranasal administration.

In another embodiment of this invention, an isolated nucleic acid molecule having the complete viral nucleotide sequence of the wild-type viruses, the vaccine viruses or the revertant viruses described herein is used to generate oligonucleotide probes (from either positive strand antigenomic message sense or

negative strand complementary genomic sense) and to express peptides (from positive strand antigenomic message sense only), which are used to detect the presence of those wild-type viruses, vaccine strains and/or revertant strains in samples of body fluids and tissues. The nucleotide sequences are used to design highly specific and sensitive diagnostic tests to detect the presence of the virus in a sample.

Polymerase chain reaction (PCR) primers are synthesized with sequences based on the viral wild-type, vaccine or revertant sequences described herein. The test sample is subjected to reverse transcription of RNA, followed by PCR amplification of selected cDNA regions corresponding to the nucleotide sequence described herein which have nucleotides which are distinct for a defined strain of virus. Amplified PCR products are identified on gels and their specificity confirmed by hybridization with specific nucleotide probes.

ELISA tests are used to detect the presence of antigens of the wild-type, vaccine or revertant viral strains. Peptides are designed and selected to contain one or more distinct residues based on the wild-type, vaccine or revertant sequences described herein. These peptides are then coupled to a hapten (e.g., keyhole limpet hemocyanin (KLH) and used to immunize animals (e.g., rabbits) for the production of monospecific polyclonal antibody. A selection of these polyclonal antibodies, or a combination of polyclonal and monoclonal antibodies can then be used in a "capture ELISA" to detect antigens produced by those viruses.

Samples of mutant RSV described herein have been deposited by Applicants' assignee on March 19, 1992 with the American Type Culture Collection (ATCC)

12301 Parklawn Drive, Rockville, Maryland, U.S.A. 20852, under the provisions of the Budapest Treaty for the Deposit of Microorganisms for the Purposes of Patent Procedures ("Budapest Treaty"). The viruses were accorded the following ATCC designation numbers: 2Bp33F(VR 2364), 2Bp24G(VR 2370), 2Bp20L(VR 2368), 2Bp34L(VR 2365), 3Ap20E(VR 2369), 3Ap20F(VR 2367), and 3Ap28F(VR 2366). In addition, samples of the 2B wild-type RSV virus were deposited by Applicants on August 21, 1997 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A., under the provisions of the Budapest Treaty and have been assigned ATCC accession number VR2586.

Given these deposited subgroup B strains and the sequence information for these and other strains provided herein, one can use site-directed mutagenesis and rescue techniques described above to introduce mutations (or restore a wild-type genotype) of all the subgroup B strains described herein, as well as taking these strains and making additional mutations from the panel of mutations set forth in Tables 21 and 22 below.

In order that this invention may be better understood, the following examples are set forth. The examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention.

Examples

Standard molecular biology techniques are utilized according to the protocols described in Sambrook et al. (76).

Example 1

Passage and Characterization of RSV 2B and RSV 3A Parental Strains

RSV 2B and RSV 3A parental strains were isolated and passed in qualified cell lines and under conditions consistent with use as clinical study material.

Two RSV strains, 20648 and 23095, were isolated by Dr. Robert Belshe (St. Louis University Health Science Center, St. Louis, MO) from nasal swab samples taken from ill children. These viruses were later recovered from the original frozen nasal swab samples, passed two to three times in primary rhesus monkey kidney (PRMK) cells, and then sent to applicants.

Isolate 20648 (subgroup B) was renamed RSV 2B. Virus was passed seven times in PRMK cells at 35°C, two times in Vero cells at 35°C and plaque purified and amplified three times (six passages) in Vero cells at 36°C. Virus was further amplified an additional two times in Vero (36°C), stocks were filtered with a 0.2 m filter and amplified another two times in Vero cells. This was followed by production of a Master Seed (RSV 2B, MK7 V12b), Intermediate working seed (RSV 2B, MK7 V13b) and Working seed (RSV 2B, MK7 V14b). See Figure 1.

Isolate 23095 (subgroup A) was renamed RSV 3A. RSV 3A was passed eight times in PRMK cells at 35°C. This was followed by two passages in Vero at 35°C and six passages in Vero cells at 36°C, including three plaque purification steps. Virus was further passaged six times in Vero cells at 36°C including a 0.2 m filtration step. This was followed by production of a Master seed (RSV 3A, MK8 V15b), Intermediate

working seed (RSV 3A, MK8 V16b), and Working seed (RSV 3A, MK8 V17b). See Figure 1.

Subgroup specificities of RSV 2B and RSV 3A Master seeds were confirmed using subgroup specific monoclonal antibodies. Virus stocks were shown to be free of microbial contaminants and adventitious agents.

The F, N, and G proteins of RSV 2B and RSV 3A stocks and reference RSV strains A2, Long, and 18537 were analyzed by radioimmunoprecipitation (RIP) and western blotting procedures using monoclonal antibodies. The F1 subunits of the RSV subgroup B strains, 2B and 18537, migrated faster on SDS-polyacrylamide gels than did the F1 subunits of the RSV subgroup A strains, 3A and Long. No difference in migration of the N proteins of the RSV 2B and 3A strains and the reference strains was seen. In RIP gels, the G protein was visible as two bands at approximately 80-90 kD and approximately 45 kD. The 80-90 kD bands of RSV 3A and Long comigrated; however, the 80-90 kD band of RSV 2B also appeared to comigrate with the subgroup A species rather than with the faster RSV 18537 (subgroup B1). This suggests that RSV 2B may be a member of the B2 subgroup as described by Akerlind (77). In western blots, the relative proportions of 80-90 kD and 45 kD bands were roughly equal for RSV Long, A2, 2B, and 18537 grown in Vero cells, but staining of the 80-90 kD band of RSV 3A was significantly greater, suggesting a difference in processing of the G protein for this strain when grown in Vero cells. These data demonstrate that the apparent M_r for the RSV 2B and RSV 3A strains are consistent with current subgroup classifications of RSV, but confirm that these strains are not identical to the prototype RSV reference strains.

Growth of RSV 2B, RSV 3A and RSV A2 in mice

and in cotton rats was compared. Both RSV 2B and RSV 3A replicated poorly in Balb/c mice compared to the RSV A2 reference strain. Consistent recovery of RSV 2B and RSV 3A could only be obtained at the highest inoculum dose used ($10^{6.0-6.2}$ PFU), and was similar in magnitude to recovery of RSV A2 at a 100-fold lower inoculum ($10^{4.3}$ PFU). In contrast, growth of RSV 2B in cotton rat nose and lungs was similar to growth of RSV A2. Growth of RSV 3A in the nose was similar to the other strains; however growth in lungs was significantly poorer. Both mouse and cotton rat growth data indicate that RSV 2B and RSV 3A have significantly different *in vivo* growth characteristics than the RSV A2 reference strain, as well as differing from each other.

Example 2

Cold Adaptation of RSV

In order to select an appropriate starting temperature for cold adaptation of RSV, growth of the RSV 2B and RSV 3A parental strains in Vero cells at temperatures ranging from 26°C to 36°C was compared. Cells were infected at an MOI of 0.4 and virus yield and CPE was monitored for four days. The results, shown in Figures 2 and 3, demonstrated that for both virus strains, growth at 30°C, 32°C, and 36°C was similar in kinetics and yield. At 26°C, virus growth lagged behind growth at the higher temperatures by about 24 hours. The limiting factor in achieving optimum titers appeared to be the viral CPE, which occurred earlier at higher temperatures. For both RSV 2B and RSV 3A, optimum titers were achieved by maintaining cultures at 30°C. At this temperature, a lower level of CPE allowed growth and spread of virus to continue over a longer time period. The results

suggested that these strains of RSV were already well adapted to growth at 30°C to 36°C. A maximum temperature of 26°C was selected as a starting temperature for cold adaptation, as virus growth at this temperature was suboptimal and therefore some selective pressure for cold adaptation would be exerted.

Cold adaptation was initiated on virus stocks RSV 2B (passage MK7 V14) and RSV 3A (passage MK8 V14). To maximize the chance of recovering appropriately attenuated mutants from these cold-adapted populations, two flasks of virus were independently passed using each of three different cold adaptation strategies. This provided a total of six cold-adapted populations for RSV 2B and six for RSV 3A. Virus was passaged in 25 cm^2 flasks containing confluent Vero cell monolayers. At each passage, virus was harvested by replacing the maintenance medium (10 mls of MEM/2%FBS/20mMHepes) in the infected flask with a reduced volume of freezing medium (3 mls of MEM/10%FBS/20mMHepes) and performing a quick freeze at -70°C followed by a thaw at 32°C. To infect the next passage, one ml of the freeze-thaw lysate was transferred to a fresh flask of confluent Vero cells, virus was allowed to adsorb at room temperature (20°C-22°C), and then flasks were overlaid with maintenance medium (MEM/2%FBS/20mMHepes) and incubated at the appropriate temperature in water baths (i.e., 26°C, 22°C, 20°C).

Titrations were performed at 32°C on each freeze-thaw lysate and the remainder of the material was stored at -70°C for future isolation of virus variants. Three passaging strategies were used. Flasks E and F were "slowly" adapted, beginning at 26°C with four passages every two days, followed by passage once every week until titers appeared to be relatively

stable or were increasing. Virus was then passaged weekly at 22°C until consistently high titers were achieved, and finally maintained by passage every 1-2 weeks at 20°C. Flasks G, H ,and I were adapted by a more moderate strategy. Virus was passaged two times at 26°C at three day intervals, then passaged weekly at 22°C five times, and finally maintained by passage every 1-2 weeks at 20°C. Flasks J and L were "rapidly" adapted, starting with five weekly passages at 22°C, followed by passage at 1-2 week intervals at 20°C. Actual passage conditions and titration results are shown in Tables 1 and 2, and are summarized in Table 3. Titration results obtained at each passage are graphically displayed in Figure 4. The titration results demonstrated an influence of strain on rate of adaptation. For RSV 2B, all three cold adaptation strategies eventually yielded high virus titers when flasks were maintained at 20°C. In contrast, RSV 3A was adapted to growth at 20°C using a "slow" strategy (E,F), but efforts to force a more rapid adaptation resulted in a precipitous decline in virus growth. Passage of these cultures (3A:H,I,J,L) was discontinued.

To screen the cold-adapted virus populations for accumulation of *ts* variants, virus taken from each flask following 5 and 17 weeks of cold adaptation was tested for efficiency of plaquing (EOP) at 39°C vs. 32°C. As seen in Table 4, in most cases plaquing efficiency of the cold passage virus was relatively high at 39°C ($\geq$0.2) and was similar to values obtained with the parental virus control ($\geq$0.6). The results showed that the cold-adapted virus populations, with the possible exception of flask RSV 3A-F, had not become predominantly *ts* over a period of up to 17 low temperature passages.

Following further cold passaging, attempts were made to isolate temperature sensitive mutants by plaque purifying virus from each cold-adapted flask. Plaque purified mutants were initially identified by relatively poor growth (lower titers or smaller plaque size) at 39°C vs 32°C. In these assays, shown in Table 5, the percentage of plaque purified virus that could be clearly identified as temperature sensitive ranged from 0% to 40% of plaques picked. Several individual flasks (2B-H, 2B-L, 3A-E, 3A-F) appeared to contain a relatively higher percent of *ts* phenotypes, and in some cases the percentage of *ts* mutants increased over time. However, *ts* mutants did not appear to become a predominant variant over a period of up to 42 weeks of cold passaging.

To summarize, cold passaging of RSV 2B and RSV 3A resulted in cold adaptation of virus based on the ability of virus to grow stably at 20°C with consistently high yields. Analysis of EOP assays and the rate of isolation of *ts* mutants indicated that although *ts* mutants did arise in the cold-adapted virus populations, they did not become a predominant species.

Example 3

Screening for Vaccine Candidates in *In Vitro* Studies

The *ts* mutants were further screened and selected for vaccine candidates based on degree of temperature sensitivity *in vitro*, attenuation in animal models (including mice, cotton rats, and chimps), and retention of neutralizing epitopes.

Over a period of 39 weeks of cold adaptation, a total of 13 RSV 2B and six RSV 3A *ts* mutants were plaque purified a second time and further characterized. Comparison of EOP's at 37/32°C,

39/32°C, and/or 40/32°C confirmed that these mutants had reduced plaquing efficiency at the higher temperatures and represented a range of temperature sensitivity (see Table 6).

Prior to completing the isolation of all 19 mutants described above, a group of four mutants, RSV 2Bp24G, RSV 2Bp20L, RSV 3Ap20E, and RSV 3Ap20F, were selected from the first set of plaque purified viruses for preliminary characterization. To look at actual virus growth curves, Vero cells were infected with these four mutants at an MOI of 2, and incubated at 20°C, 32°C, 37°C, and 40°C for seven days. The results, shown in Figure 5, indicated that all four mutants were cold-adapted and temperature sensitive, as evidenced by earlier and higher rises in titer in cultures incubated at 20°C, and reduced or absent growth of virus in cultures incubated at 37°C, 39°C, and 40°C. Based on the degree of temperature sensitivity seen in EOP and growth studies, one subgroup A and one subgroup B mutant, RSV 2Bp20L and RSV 3Ap20E, were selected to perform additional preliminary experiments on phenotypic stability and growth in mice.

The infectivity and immunogenicity of RSV 2Bp20L and RSV 3Ap20E were evaluated in Balb/c mice. Virus growth was measured in nasal wash and lung samples harvested four and five days post-infection and serum neutralizing antibody titers were determined 32 days post-infection. Results are shown in Table 7. Growth and immunogenicity of the parental virus was very low, but detectable. In contrast, no virus was recovered and no neutralizing antibody was detected following inoculation of the *ts* strains, indicating that these strains were highly attenuated in mice.

Of the 19 *ts* mutants which were eventually isolated, four RSV 2B and three RSV 3A mutants were

selected for further *in vitro* and *in vivo* characterization. These mutants included the original four mutants described above, as well as three mutants isolated at later time points. Selection criteria included demonstration of definite *ts* phenotype at both 37°C and 39°C and representation of both subgroups and varying passage strategies and passage numbers. These seven *ts* mutants were plaque purified a third time and amplified to make small working stocks. Their passage histories are summarized in Table 8. The initial analysis of these mutant strains included comparison of plaquing efficiencies and plaque morphologies at 32°C, 37°C, and 39°C in Vero cells (Table 9), and growth at 32°C, 37°C, 39°C, and 40°C in Vero cells (Table 10). At 37°C and 39°C, EOP was reduced and small and intermediate plaque sizes predominated, indicating that mutants were *ts*. Some breakthrough of "wt" plaque size revertants was seen with all variants except RSV 2Bp34L and RSV 3Ap20F.

In growth studies, Vero cells were infected with the virus strains at an MOI of 0.2 and virus yield was determined four days post-infection. Comparison of virus yields in Vero cells at the various temperatures demonstrated that virus yield, expressed as PFU per cell, decreased significantly at the higher temperatures (37°C, 39°C, 40°C). In some cases, virus yield was also somewhat reduced at 32°C relative to the parental strain, indicating attenuation in growth at 32°C. This is consistent with the smaller plaque sizes observed in the 32°C EOP assays (Table 9). For all strains, at least one plaque was detected in cells incubated at 39°C or 40°C, suggesting that some revertants were present. Both EOP and virus yield studies demonstrate that these seven isolates possess varying levels of temperature sensitivity and may

represent a range of levels of attenuation.

Retention of neutralizing epitopes was examined by comparing reactivities of the seven mutants and parental strains with two neutralizing monoclonal antibodies representing antigenic sites A and C on the F protein described by 19-Beeler and Coelingh (1989) (Table 11). Both antibodies were able to neutralize all the virus strains at similarly high dilutions, indicating that the neutralizing epitopes were intact.

Example 4
Growth of Mutant Strains in Animal Models

Growth and immunogenicity of the seven *ts* mutant strains was evaluated in cotton rats. Groups of rats were inoculated intranasally with each mutant and lungs and nasal turbinates were harvested four days post-infection for virus titrations. Sera were collected from an identical set of rats 20 days post-infection to test for neutralizing and EIA antibody responses. A summary of virus titration and immunogenicity results are shown in Table 12. RSV 2B grew well in the nose and lungs, whereas growth of all four RSV 2B *ts* mutants was very poor. Two of the mutants, RSV 2Bp33F and RSV 2Bp24G, displayed a less attenuated phenotype than did RSV 2Bp20L and RSV 2Bp34L, as indicated by a slightly higher level of replication, as well as a 100% infection rate. The RSV 3A parental and *ts* mutant strains grew well in the nasal turbinates, but poorly in the lungs. Titers of the RSV 3A *ts* mutants were lower than that of the parental strain, indicating that the *ts* mutants were somewhat more attenuated than the parent virus. Neutralizing and EIA-F antibody titers on sera from rats infected with the RSV 2B and RSV 3A parental and *ts*

mutant strains were also measured. The level of neutralizing and EIA-F antibody titer was low for the RSV 2B *ts* mutants, consistent with the low level of viral replication seen. Interestingly, titers from animals infected with RSV 2Bp33F were higher than would be expected in view of the low titration values, and may indicate an intermediate level of attenuation for this virus. Neutralizing and EIA-F antibody titrations on all 3 RSV 3A *ts* mutants demonstrated that these mutants were quite immunogenic, consistent with their high level of replication in nasal tissue.

Growth of RSV 2Bp20L was further evaluated in cotton rats from three to seven days post-infection to determine if failure to recover virus was due to a shift in timing of peak titers. RSV 2B was used as a positive control (see Figure 6). The growth kinetics of RSV 2B were typical of other strains of RSV; peak titers occurred on days 4 and 5 in nasal turbinates and on day 4 in lungs. These results substantiate the use of day 4 as the optimal harvest day for the parental strain. RSV 2Bp20L was not detected in lungs and rare plaques were seen in nasal turbinate titrations on days 3, 5, 6, and 7, demonstrating that attenuation of this virus was not simply due to an early or late growth peak.

Relative growth and immunogenicity of RSV 2B and RSV 2Bp20L were also compared in four year old seropositive chimps. Two chimps were infected intranasally with $10^{4.0}$ and $10^{5.0}$ PFU of RSV 2B, and two chimps were similarly infected with RSV 2Bp20L. The results are shown in Figure 7 and Table 13. Both chimps infected with RSV 2B developed a mild upper respiratory infection, consisting of nasal discharge and cough. Both chimps shed virus from three through seven days post-infection. The amount of virus shed

was higher and shedding occurred earlier in the chimp infected with the higher dose of RSV 2B. Neither chimp inoculated with RSV 2Bp20L showed clinical signs of disease or shed virus. Chemistry and hematology workups on all four chimps revealed no significant findings. Serum neutralizing and EIA-F, Ga, and Gb antibody titers were substantially increased 14 and 21 days post-infection with RSV 2B. No rises in antibody titers were seen in chimps inoculated with RSV 2Bp20L. The results indicated that, in seropositive chimps, the parental RSV 2B strain was infectious and immunogenic, whereas the RSV 2Bp20L mutant was highly attenuated.

Example 5

Challenge Experiments in Cotton Rat Model

Additional experiments were done in cotton rats to evaluate the efficacy of the RSV 2B and 3A *ts* mutants in preventing infection when challenged with a reference strain of the homologous subgroup (RSV 18537/subgroup B and RSV A2/subgroup A). Cotton rats (eight per group) were inoculated intranasally with each RSV *ts* mutant. Nasal turbinates and lungs were harvested four days post-infection, from four rats per group, for virus titrations. Six weeks post-infection, the remaining rats were bled for neutralizing and EIA-F titers, then challenged with the appropriate reference RSV strain. Four days post-challenge, nasal turbinates and lungs were removed for virus titration. Results are shown in Tables 14 and 15.

As discussed previously and shown in Table 12, growth of all four RSV 2B *TS* mutants was very poor compared to the parental RSV 2B strain. Neutralizing

and EIA antibody titers elicited by RSV 2Bp33F and RSV 2Bp24G were relatively high despite poor virus recovery, possibly indicating an intermediate level of attenuation for both mutants. Level of protection against virus challenge reflected the level of neutralizing antibody response and was high for RSV 2Bp33F and 2Bp24G, moderate for RSV 2Bp20L, and ineffective for RSV 2Bp34L. All RSV 3A strains grew in the nasal turbinates but demonstrated a high level of attenuation in growth in the lungs. Titers of neutralizing and EIA antibodies were high and all rats were completely protected against virus challenge.

The results demonstrate that growth of the attenuated strains elicited protective immunity against virus challenge, suggesting that these strains may be useful as vaccine. Failure of vaccination with the RSV 2Bp34L strain to protect was most likely due to failure of virus to grow due to its high level of attenuation. Since cotton rats are a less susceptible host than humans, failure of this strain to protect does not imply that 2Bp34L would be an ineffective vaccine in humans.

Example 6

Challenge Experiments in African Green Monkey Model

Growth, immunogenicity, and efficacy of *ts* mutant strains RSV 2Bp33F, 2Bp24G, 2Bp20L, 3Ap20E, 3Ap20F, and 3Ap28F were evaluated in African green monkeys (AGMs). AGMs are more susceptible to infection with human RSV than are the cotton rats, and characteristics of infection may be more relevant to that seen in humans because of the closer phylogenetic relationship. Two AGMs each were inoculated with 10^6 PFU of each mutant virus by combined intranasal and

intratracheal route. Virus growth was evaluated by nasal wash and bronchial lavage. Neutralizing and EIA antibody responses were tested at approximately 0, 1, 2, 3, 4, 6, and 8 weeks post-infection. Eight weeks post-infection, animals were challenged with 10^6 PFU of the parental strain by intranasal and intratrachial route. Virus growth and antibody response was evaluated as described above.

Growth of the parental RSV 2B and 3A strains can be seen in Figures 8 and 9: vaccine controls. Both virus strains grew to high titers in both the nose and lung. Nasal discharge and radiographic evidence of viral pneumonia was seen in one control monkey (032B) infected with RSV 2B, demonstrating that RSV is capable of causing disease in AGMs. These results confirm differences in these characteristics of infection in AGMs vs the cotton rat model, in which disease was not observed and RSV 3A was unable to replicate in the lung. Failure of the parental strains of RSV to cause disease in three of four monkeys suggests that the AGMs are not as susceptible a host as are humans.

Virus titrations for each monkey infected with the RSV 2B *ts* mutants and then challenged with the parental strain are shown in Figure 8. RSV 2Bp33F grew to low levels in the nasal wash in one of two monkeys, RSV 2Bp24G grew to low levels in nasal wash or in lungs in both monkeys. RSV 2Bp20L failed to grow. In those AGMs where the RSV 2B *ts* mutants grew, monkeys were partially to fully protected against challenge with parental strain. Tables 16 and 17 give antibody titration results obtained for each monkey post-vaccination (Table 16) and post-virus challenge (Table 17). Results show that in monkeys where virus grew, low levels of neutralizing and EIA antibody titers were seen by 2.5 weeks post-infection. Following challenge

with the parental strain, antibody titers boosted one full week earlier in vaccinated monkeys with antibody titers prior to challenge, than in vaccinated animals which failed to seroconvert or in unvaccinated controls. This demonstrated that vaccination with these *ts* mutants was sufficient to both prime the immune system and to elicit protection against virus challenge. Because these monkeys are not as susceptible to infection as humans, failure of attenuated virus to grow and to effectively immunize does not imply that virus would not be effective in a fully susceptible host (i.e. seronegative human infant).

Virus growth in AGMs infected with the RSV 3A *ts* mutants and challenged with the parental 3A strain are shown in Figure 9. All three RSV 3A *ts* mutant strains were attenuated in growth, in the order of most to least attenuated: 3Ap28F>3Ap20E>3Ap20F. Vaccination with all three *ts* mutants afforded excellent protection against virus challenge. Antibody response for monkeys vaccinated with RSV 3A *ts* mutants is shown in Table 18, and response following virus challenge is shown in Table 19. In all vaccinated AGMs, with the exception of one monkey given RSV 3Ap28F, low levels of neutralizing and EIA antibody titers were detected beginning three weeks post-vaccination. Following challenge with the parental strain, all vaccinated monkeys boosted a full week earlier than the unvaccinated controls and were protected either fully or partially from infection, demonstrating that vaccination primed the immune response and was protective. This included the one AGM in which antibody response was not detected following vaccination, indicating that measure of serum antibody response may not be fully representative of level of

protective immunity.

The results from the AGM studies again demonstrate that all six *ts* mutants tested were attenuated. Vaccination with those mutants which were able to replicate in these monkeys was efficacious in preventing infection with challenge virus.

Example 7

Degree of Attenuation

An RSV *ts* mutant, TS-1, was obtained from Dr. Brian Murphy, NIH. This *ts* mutant was originally derived from the RSV A2 strain by chemical mutagenesis and was tested in clinical trials in seronegative human infants in the 1970's. The outcome of these trials suggested that TS-1 was underattenuated and caused an unacceptable level of disease (rhinitis and otitis media) in infants. In addition, the *ts* phenotype of TS-1 partially reverted following growth in humans. Experiments have been carried out which compare growth of the RSV 2B and 3A *ts* mutants with that of the TS-1 mutant in an attempt to assess the relative *in vivo* attenuation level of the RSV 2A and 3B mutants, and to demonstrate differences between these mutants and what had been used by others in previous clinical trials. The results of the cotton rat study are shown in Table 20, and may be compared directly with the cotton rat data shown in Tables 14 and 15. The TS-1 mutant was less attenuated than the RSV 2B and 3A *ts* mutants, as can most clearly be seen by comparing growth in the lung.

A growth study in African green monkeys (AGMs) comparing TS-1 with RSV 2Bp33F and 3Ap28F was carried out and the results are shown in Figure 10. Monkeys were infected with virus either intranasally

(TS-1 and 2Bp33F) or intranasally plus intratracheally (3Ap28F). Virus was recovered in one of four monkeys infected with 2Bp33F and two of four monkeys infected with 3Ap28F. Titers were relatively low in both cases, indicating that virus was attenuated. In contrast, relatively high titers of virus were recovered in all four monkeys inoculated with TS-1. In two of four monkeys, the levels of TS-1 titers were equivalent to those seen in monkeys infected with wild type virus. TS-1 did not spread to the lungs, as would be expected for wild type virus, indicating that TS-1 was somewhat attenuated. The results clearly show that RSV 2Bp33F and 3Ap28F have different phenotypic characteristics than TS-1 and are significantly more attenuated. This higher level of attenuation is a property that is desirable for a vaccine to be administered to human infants.

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Example 8

Sequence Analyses of RSV Subgroup B Strains

The temperature-sensitive (*ts*) phenotype is strongly associated with attenuation *in vivo*; in addition, some non-*ts* mutations may also be attenuating. Identification of *ts* and non-*ts* attenuating mutations was achieved by sequence analysis and evaluation of *ts*, cold-adapted (ca), and *in vivo* growth phenotypes of RSV mutants and revertants.

The genomes of the following five RSV 2B strains have now been completely sequenced: 2B parent, 2B33F, one revertant designated 2B33F TS(+), 2B20L and one revertant designated 2B20L TS(+). The 2B33F and 2B20L strains are *ts* and ca and are described in U.S. Serial No. 08/059,444 (78), which is hereby incorporated by reference. After identifying regions

where mutations in 2B33F and 2B20L are located, nine additional isolates of 2B33F "revertants" obtained following *in vitro* passaging at 39°C and *in vivo* passaging in African Green Monkeys or chimpanzees, and nine additional isolates of 2B20L "revertants" obtained following *in vitro* passaging at 39°C have been sequenced in those regions. The *ts*, ca, and attenuation phenotypes of many of these revertants have now been characterized and assessed. Correlations between phenotype *ts*, vaccine attenuation and sequence changes have been identified.

A summary of results is presented in Tables 21-26.

Several significant observations can be drawn from these data:

a. As shown in Tables 21 (for 2B33F) and 22 (for 2B20L), there are relatively few sequence changes identified in the two mutant strains: RSV 2B33F differs from parental RSV 2B by two changes at the 3' genomic promoter region, two changes at the non-coding 5'-end of the M gene, and four coding changes plus one non-coding (poly(A) motif) change in the RNA dependent RNA polymerase coding L gene. In addition, 14 changes mapped to the SH gene alone. RSV 2B20L differs from its RSV 2B parent only at seven nucleotide positions, of which three are common with 2B33F virus, including two changes at the 3' genomic promoter and one coding change in the L gene. Two additional unique changes of 2B20L virus mapped to the coding region of the L gene. Potentially attenuating mutations at the RNA dependent RNA polymerase gene have been identified.

b. Two *ts* mutations can be identified in the L gene of the attenuated virus strains 2B33F and 2B20L:

(i) In 2B33F, a mutation at nucleotide position 9853 (A → G) leading to a coding change in L protein at amino acid 451 (Lys → Arg) is clearly associated with the *ts* and attenuation phenotypes. Reversion at this site alone in the 2B33F TS(+) 5a strain is responsible for complete restoration of growth at 39°C (Table 23) and partial reversion in attenuation in animals. This association of *ts* was also supported by partial sequence analyses of six additional "full *ts* revertants" (designated 4a, 3b, pp2, 3A, 5a, 5A) isolated from cell culture and from chimps, in which only the nucleotide 9853 mutation reverted (Tables 24-26) (note that one AGM (African Green Monkey) isolate which reverted at 9853 only partially reverted in *ts* phenotype). This amino acid 451 mutation (Lys → Arg) is amenable to stabilization in cDNA infectious clone constructs, by inserting a second mutation to stabilize the codon, thereby lessening the likelihood that it will revert back to Lys.

(ii) In 2B20L, a mutation at base 14,649 (A → G) leading to a coding change in the L protein (amino acid position 2,050, Asn → Asp) appears to be associated with the *ts* and attenuation phenotypes. This aspartic acid at the amino acid 2050 invariably reverts back (Asp → Asn) in TS(+) revertants or changes to a different amino acid (Asp → Val) by nucleotide substitution at position 14,650 (A → T) (Tables 22, 25). The above observation is based on complete sequence analysis on the TS(+) revertant R1 and partial sequence of several additional TS(+) revertants (R2, R4A, R7A, R8A) at selected regions (Table 25). An

additional mutation is seen in the R1 revertant at nucleotide postion 13,347 (amino acid 1616, Asn → Asp) associated with the above reversion. However, the effect of this mutation on the *ts* phenotype is not known; the L gene of other revertants has not been sequenced completely.

c. Three base changes are common to 2B33F and 2B20L strains of virus:

(i) A change at position 14,587 (C → T) with a corresponding change (Thr → Ile) at amino acid 2029 is present in both 2B33F and 2B20L (Tables 21,22). This nucleotide "T" substitution was found to be present in 10% of the population of the progenitor RSV2B strain and may have been preferred during the attenuation process. No wildtype base "C" was found in the 2B33F and 2B20L virus.

(ii) Two mutations are seen in the 2B33F and 2B20L 3' genomic promoter region: nucleotide 4 (C → G) and the insertion of an extra A in the stretch of A's at positions 6-11 (in antigenomic, message sense). When the sequences of selected TS(+) revertants were analyzed, these mutations were seen to have been retained in the 2B33F TS(+)5a (Table 21) and the 2B20L TS(+)R1 (Table 22) revertants. These non-coding, cis-acting mutations remained associated with partial viral attenuation.

Expression using the minireplicon RSV-CAT system for the analysis of these cis-acting changes has shown the 3' genomic promoter nucleotide 4 (C → G) change to be an upregulation of transcription/replication in this *in vitro* system when

the 2B progenitor virus or either of the 2B33F or 2B33F TS(+) provided helper L gene functions (the N, P and M2 genes are identical in these viruses).

Complementation analysis of the 2B33F 3' genomic promoter and the helper functions provided by the progenitor RSV2B virus or the 2B33F and 2B33F TS(+) viruses by this RSV-CAT minireplicon system has also been conducted. All three viruses supported both the 2B and 2B33F 3' genomic promoter mediated transcription/replication functions. However, the 2B33F and 2B33F TS(+) viruses preferred their 2B33F 3' genomic promoters. This analysis clearly shows co-evolution of 3' genomic promoter changes during the vaccine attenuation process, along with the RNA dependent RNA polymerase gene. Reversion of *ts* phenotype in the 2B33F mutant 5a by reversion of the single L protein amino acid 451 (Arg → Lys) by sequence analysis was clearly demonstrated by support of transcription/replication functions of RSV-CAT minireplicon at 37°C. The 2B33F virus did not provide helper functions to the RSV-CAT minireplicon (with 2B or 2B33F 3' genomic promoters) at 37°C.

d. A biased hypermutation of SH seen in 2B33F is present in all 2B33F revertants, regardless of phenotype, and is not seen in 2B20L, which is *ts*, ca, and attenuated. Thus, there are no data at this time that associate this mutation with any biological phenotype.

Another wild-type RSV designated 18537 was also sequenced and compared to the sequence of the wild-type RSV 2B strain. With one exception, at all the critical residues described above, the two wild-type strains were identical. For 2B, the codon ACA at nucleotides 14586-14588 encodes a Thr at amino acid

2029 of the L protein, while for 18537, the codon ATT at nucleotides 14593-14595 encodes an Ile at amino acid 2029 (the L gene start codon is at nucleotides 8509-8511 in 18537, compared to 8502-8504 in 2B).

Example 9
PCR Assay to Detect RSV

A PCR assay is used to detect the presence of RSV. PCR primers are designed and selected based on homologies to the RSV sequences described herein to be specific for all subgroup B strains, or for the individual wild-type, vaccine or revertant RSV subgroup B strains described herein. The assay is conducted by subjecting the sample to reverse transcription of RNA, followed by PCR amplification of selected cDNA regions corresponding to RSV nucleotide sequence. Amplified PCR products are identified on gels and their specificity confirmed by hybridization with specific RSV nucleotide probes.

Example 10
ELISA to Detect RSV

An ELISA test is used to detect the presence of RSV. Peptides are designed and selected based on homologies to the RSV sequences described herein to be specific for all subgroup B strains, or for individual wild-type, vaccine or revertant RSV subgroup B strains described herein. These peptides are then coupled to KLH and used to immunize rabbits for the production of monospecific polyclonal antibody. A selection of these polyclonal antibodies, or a combination of polyclonal and monoclonal antibodies is then used in a "capture ELISA" to detect the presence of an RSV antigen.

Table 1
RSV 2B Cold Adaptation

Passage #	Cumm. Time Passage Weeks	Incubation Temp °C	Incubation Time Days	Virus Yield log_{10}PFU E,F E	F
1	0.2	26	2	6.9	6.7
2	0.4	26	2	6.0	6.1
3	0.6	26	2	5.5	5.6
4	0.8	26	2	4.5	4.7
5	1.0	26	7	4.9	5.0
6	2.0	26	7	6.2	6.3
7	3.0	26	7	7.9*	7.6*
8	4.0	22	7	7.5	7.6
9	5.0	22	7	7.3	7.3
10	6.0	22	7	7.2*	7.2*
11	7.0	22	7	7.5*	7.7*
12	8.0	22	7	8.0*	7.9*
13	9.0	22	7	8.0*	7.9*
14	10.0	20	7	7.6	7.7
15	11.0	20	7	7.0	5.9
16	12.0	20	7	7.2	7.1
17	13.0	20	7	6.7	6.3
18	15.0	20	14	5.5	5.2
19	17.0	20	14	6.3	6.0
20	18.0	20	7	6.1	5.8
21	19.0	20	7	5.4	5.7
22	20.0	20	7	5.9	5.7
23	21.0	20	7	6.3	5.5
24	22.0	20	7	6.9	6.3
25	23.0	20	7	6.8	6.6
26	24.0	20	8	6.6	6.2
27	25.0	20	7	6.3	6.0
28	26.0	20	6	6.5	6.2
29	27.0	20	7	6.2	6.3
30	28.0	20	7	7.0	7.2
31	29.0	20	7	7.3	7.1
32	30.0	20	7	6.8	6.5
33	31.0	20	7	6.9	6.7
34	32.0	20	7	6.9	7.0
35	33.0	20	7	7.4	7.0
36	34.0	20	7	7.2	7.1
37	35.0	20	7	7.4	7.0
38	36.0	20	7	7.4	7.1
39	37.0	20	7	7.5	7.0
40	38.0	20	7	7.2	6.7

*Syncytial CPE seen at harvest

Table 1b
RSV 2B Cold Adaptation

		G,H			
	Cumm. Time	Incubation		Virus Yield	
Passage	Passage	Temp	Time	$\log_{10}$PFU	
#	Weeks	°C	Days	G	H
1	0.3	26	3	7.1	7.1
2	0.7	26	3	6.9	6.9
3	1.0	22	7	6.4	6.4
4	2.0	22	7	6.4	6.3
5	3.0	22	7	6.6	6.4
6	4.0	22	7	6.9	6.8
7	5.0	20	7	6.9	6.7
8	6.0	20	7	6.3	6.3
9	7.0	20	7	6.2	6.3
10	8.0	20	7	6.6	6.9
11	9.0	20	7	7.0	7.0
12	10.0	20	7	7.0	7.4
13	11.0	20	7	6.3	7.3
14	12.0	20	7	7.7	7.9
15	13.0	20	7	7.2	7.4
16	15.0	20	14	6.4	6.3
17	16.0	20	8	6.8	6.9
18	17.0	20	6	6.9	7.0
19	18.0	20	7	6.9	7.1
20	19.0	20	7	6.7	7.0
21	20.0	20	7	6.4	6.8
22	21.0	20	7	6.5	7.0
23	22.0	20	7	6.9	7.1
24	23.0	20	7	6.8	6.7
25	24.0	20	8	6.4	6.2
26	25.0	20	7	6.0	5.5
27	26.0	20	6	6.3	5.5
28	27.0	20	7	6.5	5.9
29	28.0	20	7	7.1	6.4
30	29.0	20	7	6.1	7.1
31	30.0	20	7	6.4	5.5
32	31.0	20	7	6.2	5.9
33	32.0	20	7	6.4	6.2
34	33.0	20	7	6.4	6.9
35	34.0	20	7	6.9	6.5
36	35.0	20	7	7.0	6.7
38	37.0	20	7	7.1	7.2

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Table 1c
RSV 2B Cold Adaptation

J,L

Passage #	Cumm. Time Passage Weeks	Incubation Temp °C	Incubation Time Days	Virus Yield log_{10}PFU J	Virus Yield log_{10}PFU L
1	1.0	22	7	6.8	
2	2.0	22	7	7.1	
3	3.0	22	7	6.7	
4	4.0	22	7	5.9	6.1
5	5.0	22	7	4.8	5.7
6	6.0	20	7	4.9	5.0
7	7.0	20	7	4.8	4.9
8	9.0	20	14	6.0	6.0
9	11.0	20	14	6.6	6.3
10	12.0	20	7	6.9	6.9
11	13.0	20	7	6.6	6.7
12	15.0	20	14	6.0	6.0
13	16.0	20	8	6.3	6.2
14	17.0	20	6	6.2	6.5
15	18.0	20	7	6.6	6.7
16	19.0	20	7	6.4	6.9
17	20.0	20	7	6.5	6.9
18	21.0	20	7	6.9	7.0
19	22.0	20	7	7.4	7.4
20	23.0	20	7	7.2	7.4
21	24.0	20	8	7.0	7.1
22	25.0	20	7	6.8	6.9
23	26.0	20	6	6.9	7.0
24	27.0	20	7	7.0	7.0
25	28.0	20	7	7.8	7.4
26	29.0	20	7	7.5	7.3
27	30.0	20	7	6.8	6.7
28	31.0	20	7	6.9	6.8
29	32.0	20	7	7.0	6.9
30	33.0	20	7	7.4	7.2
31	34.0	20	7	7.3	6.7
32	35.0	20	7	7.3	6.9
33	36.0	20	7	7.3	7.0
34	37.0	20	7	7.2	6.9
35	38.0	20	7	6.6	6.3

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Table 2a
RSV 3A Cold Adaptation

		E		
	Cumm. Time	Incubation		Virus Yield
Passage #	Passage Weeks	Temp °C	Time Days	log_{10}PFU E
1	0.2	26	2	6.2
2	0.4	26	2	5.1
3	0.6	26	2	4.7
4	0.8	26	2	3.8
5	1.0	26	7	4.0
6	2.0	26	7	5.0
7	3.0	26	7	6.1
8	4.0	22	7	6.0
9	5.0	22	7	5.6
10	6.0	22	7	5.8
11	7.0	22	7	5.7
12	8.0	22	7	5.9
13	9.0	22	7	5.9
14	11.0	20	14	5.8
15	13.0	20	14	6.1
16	15.0	20	14	4.8
17	17.0	20	14	4.9
18	19.0	20	14	4.8
19	20.0	20	7	4.3
20	22.0	20	14	4.9
21	24.0	20	14	5.2
22	26.0	20	15	5.6
23	28.0	20	13	6.3
24	30.0	20	14	6.3
25	32.0	20	14	7.3
26	34.0	20	14	7.8
27	36.0	20	14	7.2
28	38.0	20	14	7.4
29	40.0	20	14	6.8
30	42.0	20	14	7.3

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Table 2b
RSV 3A Cold Adaptation

		F		
	Cumm. Time	Incubation		Virus Yield
Passage #	Passage Weeks	Temp °C	Time Days	log_{10}PFU F
1	0.2	26	2	6.1
2	0.4	26	2	5.1
3	0.6	26	2	4.7
4	0.8	26	2	3.6
5	1.0	26	7	4.3
6	2.0	26	7	5.3
7	3.0	26	7	6.4
8	4.0	22	7	6.3
9	5.0	22	7	5.2
10	6.0	22	7	5.8
11	7.0	22	7	5.7
12	8.0	22	7	6.0
13	9.0	22	7	5.6
14	11.0	20	14	5.5
15	13.0	20	14	5.4
16	15.0	20	14	3.9
17	17.0	20	14	3.7
18	19.0	20	14	3.5
19	21.0	20	14	3.8
20	23.0	20	14	4.2
21	25.0	20	15	3.2
22	27.0	20	13	3.9
23	29.0	20	14	4.5
24	31.0	20	14	4.7
25	33.0	20	14	4.8
26	35.0	20	14	5.3
27	37.0	20	14	5.5
28	39.0	20	14	5.8

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Table 2c
RSV 3A Cold Adaptation

H,I

Passage #	Cumm. Time Passage Weeks	Incubation Temp °C	Incubation Time Days	Virus Yield log_{10}PFU H	Virus Yield log_{10}PFU I
1	0.3	26	3	6.9	7.0
2	0.7	26	3	6.1	6.4
3	1.0	22	7	5.8	5.8
4	2.0	22	7	5.8	5.9
5	3.0	22	7	5.9	5.7
6	4.0	22	7	5.6	5.5
7	5.0	22	7	5.1	5.1
8	6.0	20	7	4.0	3.8
9	7.0	20	7	3.3	2.8
10	9.0	20	14	3.9	3.2
11	11.0	20	14	3.9	3.1
12	13.0	20	14	4.0	3.0

J,L

Passage #	Cumm. Time Passage Weeks	Incubation Temp °C	Incubation Time Days	Virus Yield log_{10}PFU J	Virus Yield log_{10}PFU L
1	1.0	22	7	6.7	
2	2.0	22	7	6.7	
3	3.0	22	7	6.0	
4	4.0	22	7	5.7	5.6
5	5.0	22	7	4.2	4.9
6	6.0	20	7	3.7	3.7
7	7.0	20	7	3.1	3.0
8	9.0	20	14	2.8	3.2
9	11.0	20	14	2.3	3.3
10	13.0	20	14	3.0	2.8

replacement sheet

Table 3
Summary of Cold Adaptation Passage History

	#Parental Virus Passage				# Cold Adaptation Passage				
	PRMK	Vero			Vero				
Virus	35°C	35°C	36°C	Total	Flask	26°C	22°C	20°C	Total
2B	7	2	12	21	E,F	7	6	27	40
					G,H	2	5	32	39
					J,L	0	5	30	35
3A	8	2	12	22	E	7	6	17	30
					F	7	6	15	28
					H,I	2	5	5	12
					J,L	0	5	5	10

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Table 4
Efficiency of Plaquing of Cold Passaged Virus

Virus	Week 5	Week 17
2B	0.8	0.6
2B-E	0.6	0.6
2B-F	0.8	0.7
2B-G	0.6	0.8
2B-H	0.7	0.4
2B-J	ND	0.9
2B-L	0.7	0.6
3A	0.6	0.6
3A-E	0.6	0.4
3A-F	0.8	0.2
3A-H	0.6	ND
3A-I	0.9	ND
3A-J	0.6	ND
3A-L	0.6	ND

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Table 5

TS Mutants Plaque Purified from Cold Adapted Virus

Cumm./Passage Weeks #	#TS/#Total Plaques Isolated		Cumm./Passage Weeks #	#TS/#Total Plaques Isolated
	E	F		E
wk23/p25	0/10	1/10	wk22/p20	2/10
wk31/p33	0/10	1/10	wk32/p25	1/10
wk38/p40	0/10	1/10	wk42/p30	3/9
	G	H		F
wk23/p24	1/10	2/10	wk23/p20	1/9
wk31/p32	0/10	2/10	wk31/p24	0/10
wk38/p39	1/10	4/10	wk37/P27	1/10
			wk39/p28	2/5
	J	L		
wk23/p20	0/9	1/10		
wk31/p28	0/10	0/10		
wk37/p34	0/8	2/9		
wk38/p35	1/20	3/8		

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Table 6

Summary of EOP Data on Twice Plaque Purified RSV TS Mutants

RSV Isolate		EOP 37/32°C	EOP 39/32°C	EOP 40/32°C
2B	(parent)	0.7-1.0	0.6-0.8	0.4
2Bp33F	(pp10-1)	0.5	0.002	ND
2Bp40F	(pp7-20).		0.0008	ND
2Bp24G	(pp2-1)	0.2	0.00001	<0.00001
2Bp39G	(pp7-3)	1.0	0.009	ND
2Bp24H	(pp3-2)	ND	0.003	0.001
2Bp32H	(pp6-2)	0.9	0.03	ND
2Bp39H	(pp6-5)	1.0	0.04	ND
2Bp35J	(pp2-1)	0.4	0.2	ND
2Bp20L	(pp5-1)	0.02	ND	<0.00001
2Bp34L	(pp2-2)	0.005	0.0005	ND
2Bp35L	(pp1-1)	0.3	0.02	ND
2Bp35L	(pp2-1)	0.5	0.1	ND
2Bp35L	(pp8-3)	0.2	0.05	ND

RSV Isolate		EOP 37/32°C	EOP 39/32°C	EOP 40/32°C
3B	(parent)	1.0	0.5-0.9	0.6
3Ap20E	(pp3-1)	0.6	0.006	0.000009
3Ap25E	(pp7-5)	0.5	0.2	ND
3Ap30E	(pp3-1)	0.4	0.08	
3Ap20F	(pp4-3)	0.8	>0.1	0.000004
3Ap27F	(pp1-2)	0.3	0.003	ND
3Ap28F	(pp10-1)	0.2	0.002	ND

ND = Not Done

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Table 7

RSV Infection of BALB/c Mice: Attenuation and Immunogenicity

Virus Strain	Dose Log_{10}Pfu	Infection Rate	Nasal Wash Log_{10}PFUml day 4	Nasal Wash Log_{10}PFUml day 5	Lung Tissue Log_{10}PFU/G day 4	Lung Tissue Log_{10}PFU/G day 5	Antibody Titers' Neut. 2B	Neut. 3A	Neut. A2
2B (parental)	6.2	8/8+	2.0	1.9	2.8	2.0*	17	21	<8
2B-CAp20L	6.3	0/8	N.P.	N.P.	N.P.	N.P.	<8	<8	<8
3A (parental)	6.0	8/8	1.4	0.5*	2.3*	2.6	19	57	11
3A-Cap-20E	6.5	0/8	N.P.	N.P.	N.P.	N.P.	<8	<8	<8
Vero	---	0/8	N.P.	N.P.	N.P.	N.P.	<8	<8	<8

N.P. = No plaques

* = Values are below optimal detection limits of assay based on a minimum of 1 plaque per well.

\+ = Sera was taken 32 days post-infection.

Neutralization results are expressed as the reciprocal of the dilution giving 60% plaque reduction neutralization, again RSV 2B, 3A, and A2

F = Infection rate = # of mice positive for RSV/Total # of mice inoculated.

Table 8
Sumary of RSV TS Mutant Passage History

	# Vero Passage						
		Adaptation and Plaque Purification (x3) (parental virus)		Cold Adaptation			Plaque Purification (x3) + expansion
Virus	PRMK 35°C	35°C	36°C	26°C	22°C	20°C	32°C
2Bp33F pp10-1-2	7	2	12	7	6	20	6
2Bp24G pp2-1-1	7	2	12	2	5	17	5
2Bp20L pp5-1-1	7	2	12	-	5	15	5
2Bp34L pp2-2-2	7	2	12	-	5	29	5
3Ap20E pp3-1-1	8	2	12	7	6	7	5
3Ap20F pp4-3-1	8	2	12	7	6	7	5
3Ap28F pp10-1-2	8	2	12	7	6	15	5

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Table 9
EOP and Plaque Morphology of RSV 2B and RSV 3A TS Mutants in Vero Cells

VIRUS	TEMPERATURE (°C)	EOP	PLAQUE MORPHOLOGY OBSERVATIONS
2B	32°	1.0	99% WT
	37°	0.9	H, Most WT
	39°	0.6	99% WT
2Bp33F pp10-1-2, V+3	32°	1.0	1/3 SP, I, WT
	37°	0.01	Mostly SP, F
	39°	0.00005	95% SP, D, Few WT
2BP24G pp2-1-1, V+3	32°	1.0	1/3 SP, I, WT
	37°	0.09	H, SP and I
	39°	0.004	1/3 SP, I, WT
2Bp20L pp5-1-1, V+4 0.0002	32°	1.0	H, 1/3 WT
	37°	0.01	1/3, SP, I, WT
	39°	0.0002	1/3 SP, I, WT
2Bp34L pp2-2-2,V+3	32°	1.0	H, Mostly I
	37°	0.002	Mostly SP, F
	39°	0.0001	Very SP, No WT

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Table 9 (continued)
EOP and Plaque Morphology of RSV 2B and RSV 3A TS Mutants in Vero Cells

VIRUS	TEMPERATURE (°C)	EOP	PLAQUE MORPHOLOGY OBSERVATIONS
3A	32°	1.0	99% WT
	37°	0.9	Mostly WT
	39°	0.5	Mostly WT
3Ap20E pp3-1-1, V+4	32°	1.0	Mostly I
	37°	0.8	Mostly I, 1/3 SP
	39°	0.04	95% SP, I, F, Few WT
3Ap20F pp4-3-1, V+3	32°	1.0	Mostly I and WT
	37°	0.7	Mostly I and WT
	39°	0.1	Mostly SP, I, No WT
3Ap28F pp10-1-2, V+3	32°	1.0	Mostly SP and I
	37°	0.4	Mostly I, F, Few WT
	39°	0.01	90% SP, I, F, Few WT

****

Abbreviations:

SP	Small Plaque
I	Intermediate
WT	Wild Type
D	Dark Stained
F	Faint Stained
H	Heterogeneous

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Table 10
Temperature-Related Growth of RSV 2B and 3A strains
in Vero Cells: Four Day Virus Yields

Virus	Virus Yield PFU/Cell 32°C	37°C	39°C	40°C
2B	0.8	0.6	0.4	0.1
2BP33F pp10-1-2,V+3	0.5	0.01	≤0.00008	<0.000005
2Bp24G pp2-1-1, V+3	1.0	0.08	0.0003	0.00001
2Bp20L pp5-1-1, V+4	0.5	0.01	0.00003	0.000007
2Bp34L pp2-2-2,V+3	0.008	<0.000005	<0.000005	≤0.000007
3A	1.6	0.3	0.08	0.05
3Ap20E pp3-1-1,V+4	0.2	0.02	≤0.000006	<0.000006
3Ap20F pp4-3-1, V+3	0.5	0.05	0.00005	<0.000006
3Ap28F pp10-1-2,V+3	0.2	0.006	≤0.000006	<0.000006

Table 11

Monoclonal Antibody Neutralization of

RSV 2B and RSV 3A Parental and TS Mutants

	Neutralization Titers	
Challenge Strains	143-6C	133-1H
2B	15,091	46,775
2Bp33F	23,364	32,690
2Bp24G	>25,600	32,571
2Bp20L	25,972	32,790
2Bp34L	16,757	77,172
3A	99,814	46,493
3Ap20E	76,203	>25,600
3Ap20F	69,513	13,743
3Ap28F	80,436	34,136

Neutralizations were done by a standard 60% plaque reduction neutralization assay on Vero cell monolayers in 96-well microtiter plates. Challenge with a 1:400 dilution of non-neutralizing monoclonal antibody 131-2G showed no reduction in titer in any of the nine strains.

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Table 12
RSV TS Mutant Infection of Cotton Rats - 4 Days Post-Infection

	Virus Growth					Immunogenicity*					
Virus Strain	Dose Log_{10} Pfu	Infection Rate	Log_{10} Nasal	GMT+ PFU/gm Lung	Sero(+) Rate	Challenge Virus RSV 28	RSV A2	RSV 3A	EIA-F	EIA-Ga	EIA-Gb
2B	6.5	4/4	5.48 (0.19)	5.00 (0.42)	4/4	2.80 (0.36)	2.26 (.052)	3.42 (0.40)	3.43 (0.14)	≤1.95 (0.30)	3.23 (0.13)
2Bp33F	7.3	4/4	1.88 (.028)	<1.30 (0.12)	4/4	2.24 (0.22)	1.86 (0.48)	2.95 (0.25)	2.76 (0.26)	<1.70	2.33 (0.25)
2Bp24G	6.9	4/4	1.73 (0.33)	≤1.30 (0.08)	4/4	1.58 (0.23)	≤1.05 (0.05)	2.33 (0.24)	2.62 (0.34)	≤1.71 (0.01)	2.10 (0.32)
2Bp20L	7.0	0/4	<1.92 (0.11)	<1.30 (0.12)	2/3	≤1.26 (0.24)	≤1.01 (0.02)	≤1.25 (0.31)	≤2.05 (0.32)	<1.70	<1.70
2Bp34L	5.6	1/4	≤1.73 (0.05)	<1.33 (0.10)	1/3	≤1.03 (0.06)	<1.00	≤1.08 (0.08)	<1.70	<1.70	<1.70
3A	6.3	4/4	5.70 (0.23)	2.00 (0.42)	4/4	2.31 (0.13)	2.28 (0.28)	3.12 (0.31)	3.55 (0.18)	2.28 (0.29)	≤1.93 (0.46)
3Ap20E	6.5	4/4	4.97 (0.22)	≤1.40 (0.22)	4/4	2.09 (0.05)	1.74 (0.09)	2.59 (0.16)	3.40 (0.18)	2.61 (0.58)	2.18 (0.32)
3Ap20F	6.7	4/4	4.95 (0.13)	≤1.70 (0.29)	4/4	2.40 (0.41)	2.59 (0.26)	3.32 (0.39)	3.62 (0.12)	2.88 (0.33)	2.57 (0.47)
3Ap28F	6.4	4/4	3.98 (0.86)	≤1.40 (0.05)	4/4	2.12 (0.64)	1.90 (0.44)	2.73 (0.36)	3.28 (0.36)	2.45 (0.16)	≤1.83 (0.22)

+ GMT = geometric mean titer

* Sera obtained from animals three weeks post-infection.
PRINT is a 60% plaque reduction neutralization test.
EIA-F, Ga, Gb are enzyme immunoassays testing reactivity of sera with purified F protein (from RSV A2), purified Ga (from RSV A2, and purified Gb (from RSV 18537).

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Table 13
RSV Infection of Seropositive Chimps

			NEUTRALIZATION TITERS[1] (LOG_{10})			EIA TITERS[2] (LOG_{10})		
VIRUS	DOSE	DAY	2B	3A	A2	ETA-F	EIA-Ga	EIA-Gb
RSV 2B	4.0 PFU	-1	2.0	2.1	2.0	4.1	3.6	2.9
		7	2.7	2.4	2.4	4.2	3.4	3.1
		14	5.0	5.1	5.0	6.6	5.4	5.2
		21	4.9	5.0	4.9	6.5	5.3	5.2
		D21/D-1*	2.9	2.9	2.9	2.4	1.7	2.3
RSV2B	5.0 PFU	-1	2.4	2.8	2.8	4.6	4.3	3.5
		7	2.9	3.2	3.0	4.9	4.3	3.5
		14	5.0	5.1	>5.1	6.5	5.5	4.7
		21	4.8	5.4	4.9	6.4	5.8	5.3
		D21/D-1	2.4	2.6	2.1	1.8	1.5	1.8
RSV 2Bp20L	4.0 PFU	-1	2.1	2.7	2.1	4.2	3.7	2.7
		7	2.2	2.4	2.0	4.2	3.8	2.6
		14	2.0	2.4	1.9	4.1	3.8	2.6
		21	2.2	2.8	2.4	4.1	3.7	2.8
		D21/D-1	0.1	0.1	0.3	-0.1	0.0	0.1
RSV 2Bp20L	5.0 PFU	-1	1.8	2.6	2.3	3.8	4.0	3.0
		7	1.8	2.2	2.2	3.7	3.9	2.8
		14	2.2	2.5	1.9	3.8	3.9	2.7
		21	2.4	2.5	2.1	3.9	4.0	3.0
		D21/D-1	0.6	-0.1	-0.2	0.1	0.0	0.0

1 = 60% plaque reduction neutralization assay performed against RSV strain 2B, 3A, + A2.
2 = Enzyme immunoassay testing testing reactivity purified RSV.
Source of protein = F(RSV A2), Ga(RSV A2), Gb(RSV 18537).
* Rise in titer day - 1 to day 21.

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Table 14

Growth, Immunogenicity, and Efficacy of RSV 2B *ts* Mutants in Cotton Rats[1]

			Virus Titer (log_{10} PFU/gm)		Immunogenicity Neutralization[2]				Challenge Virus Titer (log_{10} PFU/gm)		
Virus	Dose	#RSV+	Nose	Lung	A2	3A	2B	EIA-F[2]	#RSV+	Nose	Lung
2B	6.1	4/4	≤3.1	4.6	174	502	521	1911	1/3	≤2.0	≤1.8
2Bp33F	5.8	2/4	≤1.2	<1.1	35	115	145	1041	1/4	<1.8	≤1.8
2Bp24G	6.4	2/4	≤1.3	≤1.0	92	201	377	2432	0/4	<1.7	<1.4
2Bp20L	6.2	0/4	<1.3	<1.0	41	123	75	482	3/4	≤2.6	3.1
2Bp34L	5.2	0/4	<1.3	<1.1	<10	<10	<10	≤77	4/4	4.8	5.4
PBS					<10	<10	<10	<50	4/4	4.9	5.5

1 = Cotton rats were inoculated with virus by intranasal route. Four days post-infection, lungs and nasal turbinates were harvested for virus titrations. Six weeks post-infection, blood was taken for neutralization and EIA titrations and rats were challenged intranasally with 10^6 PFU of RSV 18537. Lungs and nasal turbinates were harvested 4 days post-challenge. Virus and antibody titers are reported as geometric mean titers.

2 = 60% plaque reduction neutralization test.

3 = Source of coating protein is RSV A2 F protein.

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Table 15

Growth, Immunogenicity, and Efficacy of RSV 3A *ts* Mutants in Cotton Rats[1]

			Virus Titer (log_{10} PFU/gm)		Immunogenicity Neutralization[2]				Challenge Virus Titer (log_{10} PFU/gm)		
Virus	Dose	#RSV+	Nose	Lung	A2	3A	2B	EIA-F[2]	#RSV+	Nose	Lung
3A	6.0	4/4	3.2	<4.1	35	141	35	1202	0/3	<1.6	<1.4
3Ap20E	6.0	4/4	≤3.2	≤1.4	≤17	85	66	646	0/4	<1.6	<1.3
3Ap20F	6.0	4/4	3.7	<1.3	≤23	87	55	708	0/4	<1.8	<1.2
3Ap28F	6.0	3/4	≤2.3	<1.4	47	282	123	2188	0/4	<1.6	<1.4
PBS					<10	<10	<10	<50	4/4	5.6	5.6

1 = Cotton rats were inoculated with virus by intranasal route. Four days post-infection, lungs and nasal turbinates were harvested for virus titrations. Six weeks post-infection, blood was taken for neutralization and EIA titrations and rats were challenged intranasally with 10^6 PFU of RSV A2.
Lungs and nasal turbinates were harvested 4 days post-challenge. Virus and antibody titers are reported as geometric mean titers.

2 = 60% plaque reduction neutralization test.

3 = Source of coating protein is RSV A2 F protein.

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Table 16
RSV Growth and Immunogenicity in African Green Monkeys: RSV 2B *ts* Mutants[1]

		ts Mutant Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3] ($\times 10^3$)
Virus	AGM	Nasal	Lung	Day	2B	A2	3A	anti-F
2Bp33F	SK034	<0.7	<0.7	0	<10	<10	<10	<0.15
				7	<10	<10	<10	<0.15
				14	<10	<10	<10	0.88
				24	<10	<10	<10	0.49
				27	<10	<10	<10	0.92
				41	<10	<10	<10	0.26
2Bp33F	SK028	2.9	<0.7	0	<10	<10	<10	<0.15
				7	<10	<10	<10	<0.15
				14	<10	<10	<10	<0.15
				24	28	<10	<10	2.92
				27	33	<10	<10	3.56
				41	19	<10	11	1.74
2Bp24G	SK012	<0.7	1.9	0	<10	<10	<10	<0.15
				7	<10	<10	<10	<0.15
				14	<10	<10	<10	<0.15
				24	12	<10	<10	14.91
				27	10	<10	<10	13.18
				41	<10	<10	<10	11.05

1 = All monkeys were inoculated with 10^6 PFU of RSV 2B *ts* virus, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

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Table 16 (continued)
RSV Growth and Immunogenicity in African Green Monkeys:
RSV 2B *ts* Mutants[1]

		ts Mutant Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3] (x10[3])
Virus	AGM	Nasal	Lung	Day	2B	A2	3A	anti-F
2Bp24G	SK030	3.2	<0.7	0	<10	<10	<10	<0.15
				7	<10	<10	<10	<0.15
				14	<10	<10	<10	<0.15
				24	440	10	204	34.13
				27	404	21	190	37.64
				41	256	<10	98	17.74
2Bp20L	SK033	<0.7	<0.7	0	<10	<10	<10	0.24
				7	<10	<10	<10	0.30
				14	<10	<10	<10	1.48
				24	<10	<10	<10	1.64
				27	<10	<10	<10	1.24
				41	<10	<10	<10	0.34
2Bp20L	SK042	<0.7	<0.7	0	<10	<10	<10	<0.15
				7	<10	<10	<10	<0.15
				14	<10	<10	<10	<0.15
				24	<10	<10	<10	1.64
				27	<10	<10	<10	0.20
				41	<10	<10	<10	0.15

1 = All monkeys were inoculated with 10^6 PFU of RSV 2B *ts* virus, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

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Table 17
RSV Growth and Immunogenicity in African Green Monkeys:
RSV 2B Challenge of Monkeys 8 Weeks Post-Vaccinated with
RSV 2B *ts* Mutants[1]

Vaccine Virus	AGM	Challenge Virus Growth: Peak Virus Titer (log10 PFU/ml) Nasal	Lung	Immunogenicity: Day	Neutralization Titers[2]: 2B	A2	3A	EIA Titers[3] (x10^3) anti-F
2Bp33F	SK034	5.7	5.0	0	<10	<10	<10	0.52
				7	<10	<10	<10	0.91
				14	451	10	472	303.84
				21	6797	33	829	592.61
				28	4353	50	815	135.85
				42	1978	44	264	52.76
2Bp33F	SK028	<0.8	3.8	0	13	<10	<10	2.50
				7	208	65	576	43.64
				14	2868	443	2051	131.70
				21	1883	404	2344	144.39
				28	1127	227	2797	53.22
				42	941	79	729	43.30
2Bp24G	SK012	3.9	3.2	0	<10	<10	<10	21.58
				7	281	111	323	258.89
				14	604	431	731	551.49
				21	698	298	692	668.50
				28	357	325	985	189.81
				42	272	82	895	104.16

1 = AGMs were previously vaccinated with RSV 2B *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 2B, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

Table 17 (continued)
RSV Growth and Immunogenicity in African Green Monkeys:
RSV 2B Challenge of Monkeys 8 Weeks Post-Vaccinated with
RSV 2B *ts* Mutants[1]

Vaccine Virus	AGM	Challenge Virus Growth: Peak Virus Titer (log10 PFU/ml) Nasal	Lung	Immunogenicity: Day	Neutralization Titers[2]: 2B	A2	3A	EIA Titers[3] ($x10^3$) anti-F
2Bp24G	SK030	<0.8	<0.7	0	91	<10	69	34.55
				7	628	322	1120	174.07
				14	1617	397	1953	203.58
				21	1184	256	968	145.71
				28	851	276	1313	49.28
				42	637	48	329	27.36
2Bp20L	SK033	5.3	4.5	0	<10	<10	<10	1.78
				7	<10	<10	<10	1.88
				14	516	<10	325	289.94
				21	500	22	550	418.91
				28	783	56	525	148.25
				42	518	48	442	91.39
2Bp20L	SK042	5.4	3.3	0	<10	<10	<10	0.21
				7	<10	<10	<10	0.32
				14	36	<10	116	135.80
				21	213	21	284	116.99
				28	256	30	300	30.06
				42	516	40	289	19.30

1 = AGMs were previously vaccinated with RSV 2B *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 2B, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

Table 17 (continued)

RSV Growth and Immunogenicity in African Green Monkeys: RSV 2B Challenge of Monkeys 8 Weeks Post-Vaccinated with RSV 2B *ts* Mutants[1]

		Challenge Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3]
Vaccine Virus	AGM	Nasal	Lung	Day	2B	A2	3A	($x10^3$) anti-F
Control	SK046	5.9	4.7	0	<10	<10	<10	0.10
				7	<10	<10	<10	0.13
				14	272	50	594	275.33
				21	488	98	1140	587.93
				28	1377	75	1393	190.49
				42	1659	47	573	183.97
Control	032B	5.5	3.9	0	<10	<10	<10	0.25
				7	<10	<10	<10	0.24
				14	2462	201	3458	626.57
				21	1546	303	1279	482.31
				28	1162	104	1729	164.53
				42	1044	83	689	75.1

1 = AGMs were previously vaccinated with RSV 2B *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 2B, IN+IT.

2 = 60% plaque reduction neutralization test.

3 = Source of coating protein is RSV A2 F protein.

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Table 18
RSV Growth and Immunogenicity in African Green Monkeys: RSV 3A *ts* Mutants[1]

		ts Mutant Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3] (x10[3])
Virus	AGM	Nasal	Lung	Day	2B	A2	3A	anti-F
3Ap20E	01128	1.7	1.3	0	<10	<10	<10	<0.05
				7	<10	<10	<10	<0.05
				14	<10	<10	<10	3.72
				21	38	<10	39	23.12
				28	21	<10	13	27.42
				40	14	<10	<10	31.11
3Ap20E	0L1161	2.3	2.9	0	<10	<10	<10	<0.05
				7	<10	<10	<10	<0.05
				14	<10	<10	30	5.84
				21	14	12	57	19.51
				28	56	18	126	27.53
				40	44	31	108	38.90
3Ap20F	90B037	3.2	<1.0	0	<10	<10	<10	<0.05
				7	<10	<10	<10	<0.05
				14	<10	<10	11	1.17
				21	12	<10	47	34.32
				28	20	17	86	31.58
				40	49	26	123	35.05

1 = All monkeys were inoculated with 10^6 PFU of RSV 3A *ts* virus, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

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Table 18 (continued)
RSV Growth and Immunogenicity in African Green Monkeys:
RSV 3A *ts* Mutants[1]

		ts Mutant Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3] ($x10^3$)
Virus	AGM	Nasal	Lung	Day	2B	A2	3A	anti-F
3Ap20F	90B045	3.9	1.0	0	<10	<10	<10	0.35
				7	<10	<10	<10	0.30
				14	<10	<10	19	3.16
				21	11	11	22	12.61
				28	12	13	24	16.82
				40	24	<10	39	14.92
3Ap28F	91B027	2.0	<0.8	0	<10	<10	<10	<0.05
				7	<10	<10	<10	<0.05
				14	<10	<10	<10	0.18
				21	<10	<10	<10	1.29
				28	<10	<10	<10	2.63
				40	<10	11	27	3.83
3Ap28F	91B043[4]	2.9	<0.9	0	<10	<10	<10	<0.05
				7	<10	<10	<10	<0.05
				14	<10	11	27	3.83

1 = All monkeys were inoculated with 10^6 PFU of RSV 3A *ts* virus, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.
4 = Monkey died on day 15. Cause of death unrelated to RSV infection.

DEFENDANT'S EXHIBIT

Table 19
RSV Growth and Immunogenicity in African Green Monkeys: RSV 3A Challenge of Monkeys 8 Weeks Post-Vaccinated with RSV 3A *ts* Mutants[1]

Vaccine Virus	AGM	Challenge Virus Growth: Peak Virus Titer (log10 PFU/ml) Nasal	Lung	Immunogenicity: Day	Neutralization Titers[2] 2B	A2	3A	EIA Titers[3] ($x10^3$) anti-F
3Ap20E	01128	1.4	0.7	0	14	12	<10	35.75
				7	216	281	602	699.10
				14	417	265	784	611.24
				21	289	307	573	247.16
				28	263	289	731	463.57
				42	145	141	426	285.47
3Ap20E	0L1161	2.2	<0.8	0	21	<10	56	25.37
				7	526	412	2735	535.05
				14	516	521	2382	252.93
				21	581	473	1840	275.32
				28	478	437	1651	244.01
				42	250	239	753	141.33
3Ap20F	90B03	<1.1	<0.8	0	84	56	221	41.17
				7	2374	2093	6051	435.25
				14	3701	2916	8652	450.55
				21	2933	2224	6561	481.99
				28	1849	1588	4031	287.28
				42	3086	967	3950	207.98

1 = AGMs were previously vaccinated with RSV 3A *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 3A, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

Table 19 (continued)
RSV Growth and Immunogenicity in African Green Monkeys:
RSV 3A Challenge of Monkeys 8 Weeks Post-Vaccinated with RSV 3A *ts* Mutants[1]

		Challenge Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3]
Vaccine Virus	AGM	Nasal	Lung	Day	2B	A2	3A	(x10^3) anti-F
3Ap20F	90B045	<1.0	<0.8	0	24	12	56	13.44
				7	644	627	1381	182.99
				14	1024	549	2174	223.70
				21	1835	699	2130	273.87
				28	831	318	1499	177.21
				42	534	258	1073	127.80
3Ap28F	91B027	<1.0	0.8	0	<10	<10	<10	5.50
				7	408	229	521	150.97
				14	585	560	2016	234.25
				21	449	311	1161	359.53
				28	316	400	714	184.91
				42	242	217	436	142.67
Control	91K041	5.0	4.7	0	<10	<10	<10	<0.05
				7	<10	<10	<10	0.13
				14	19	<10	205	213.29
				21	106	33	423	602.54
				28	123	99	278	562.05
				42	107	80	277	252.99

1 = AGMs were previously vaccinated with RSV 3A *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 3A, IN+IT.
2 = 60% plaque reduction neutralization test.
3 = Source of coating protein is RSV A2 F protein.

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Table 19 (continued)

RSV Growth and Immunogenicity in African Green Monkeys: RSV 3A Challenge of Monkeys 8 Weeks Post-Vaccinated with RSV 3A *ts* Mutants[1]

		Challenge Virus Growth		Immunogenicity				
		Peak Virus Titer (log10 PFU/ml)			Neutralization Titers[2]			EIA Titers[3]
Vaccine Virus	AGM	Nasal	Lung	Day	2B	A2	3A	(x10^3) anti-F
Control	91K059	5.1	4.6	0	<10	<10	<10	<0.05
				7	<10	<10	<10	0.09
				14	97	34	384	166.59
				21	288	158	1259	268.47
				28	<160	<160	575	286.52
				42	290	178	1448	218.74

1 = AGMs were previously vaccinated with RSV 3A *ts* strains. All monkeys were challenged 8 weeks post-vaccination with 10^6 PFU of RSV 3A, IN+IT.

2 = 60% plaque reduction neutralization test.

3 = Source of coating protein is RSV A2 F protein.

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Table 20

Growth, Immunogenicity, and Efficacy of RSV TS-1 Cotton Rats[1]

			Virus Titer (log_{10} PFU/gm)		Immunogenicity Neutralization[2]				Challenge Virus Titer (log_{10} PFU/gm)		
Virus	Dose	#RSV+	Nose	Lung	A2	3A	2B	EIA-F[2]	#RSV+	Nose	Lung
A2	5.5	4/4	3.6	4.0	234	367	188	1259	0/4	<1.8	<1.3
TS-1	5.9	4/4	≤2.7	2.3	100	385	181	2071	0/3	<1.9	<1.3
PBS					<10	<10	<10	<50	4/4	4.5	4.8

1 = Cotton rats were inoculated with virus by intranasal route. Four days post-infection, lungs and nasal turbinates were harvested for virus titrations. Six weeks post-infection, blood was taken for neutralization and EIA titrations and rats were challenged intranasally with 10^6 PFU of RSV A2.
Lungs and nasal turbinates were harvested 4 days post-challenge. Virus and antibody titers are reported as geometric mean titers.

2 = 60% plaque reduction neutralization test.

3 = Source of coating protein is RSV A2 F protein.

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Table 21

Sequence comparison between RSV 2B and 2B33F strains

	Nucl. pos.†	Nucleotide changes			
Gene/ region	3' end of vRNA	RSV 2B	RSV 2B33F	RSV 2B33F TS(+), 5a revertant	Amino acid changes
Genomic Promoter	4 6	C -	G extra A	G extra A	non-coding non-coding
M	4175 4199	T T	C C	C C	non-coding non-coding
SH	4329 4409 4420 4442 4454 4484 4497 4505 4525 4526 4542 4561 4575 4598	T T T T T T T T T T T T T T	C C C C C C C C C C C C C C	C C C C C C C C C C C C C C	Phe-Leu (10) none Ile (36) Ile-Thr (40) none His (47) none Cys (51) none Tyr (61) Stop-Gln (66) none Ser (68) Ile-Thr (75) Ile-Thr (75) Stop-Gln (81) Leu-Pro (87) Trp-Arg (92) none Thr (99)
L	9559 9853* 12186 14587 15071	G A G C A	A G A T G	A A A T G	Arg-Lys (353) Lys-Arg (451)* Asp-Asn (1229) Thr-Ile (2029) non-coding

† For 2B33F and 2B33F TS(+), nucl. pos. numbers are one larger than for 2B for M, SH & L genes

* At pos. 9853, the Lys-Arg change has reverted back to Lys in the 2B33F TS(+) strain

Table 22

Sequence comparison between RSV 2B and 2B20L strains

	Nucl. pos.†	Nucleotide changes			
Gene/ region	3' end of vRNA	RSV 2B	RSV 2B20L	RSV 2B20L TS(+), R1 revertant	Amino acid changes
Genomic Promoter	4 6	C -	G extra A	G extra A	non-coding* non-coding*
L	8963 13347 14587 14649 14650	C A C A A	T A T G A	T G T G T	none Thr (154) Asn-Asp (1616) Thr-Ile(2029)* Asn-Asp (2050) Asn-Asp-Val (2050)**

† For 2B20L and 2B20L TS(+), nucl. pos. numbers are one larger than for 2B for L gene

* Mutation is common in 2B33F and 2B20L strains

** At pos. 14650, the mutation suppresses the *ts* phenotype in 2B20L TS(+) revertant

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DESIRED CLAUSE

Table 23

RSV 2B, *ts* and Revertant Strains

Sample	Source	*In Vitro* Phenotype		*In Vivo* Growth[a] Cotton Rat		AGM	
		ts	ca				
		39/32°C EOP plaque morph	20/32°C Yield	Nasal turbinates	Lungs	Nasal Wash	Bronchial Lavage
RSV 2B	Wild-type Parent Strain	0.7 (WT)	0.0001	5.5[a] 3.9[b] (4/4)	5.8[a] 5.2[b] (4/4)	5.8[a] (4/4)	4.7[a] (4/4)
RSV 2B33F	ca, *ts* mutant isolated from 2B cold-passaged x 33	0.00007 (ap/int/wt)	0.04	≤1.6[a] <1.9[b] (1/4)	<1.5[a] <1.2[b] (0/4)	3.0[a] (4/4)	<0.9[a] (0/4)
RSV 2B33F - 5a TS(+)	2B33F spinner passage, plaque picked at 39°C	0.5 (WT)	0.03	≤1.7[a] (1/4)	3.5[a] (4/4)	4.2[a] (4/4)	4.0[a] (4/4)
RSV 2B33F - 4a TS(+)	2B33F spinner passage, plaque picked at 39°C	0.7 (WT)	0.01	≤1.7[a] (3/4)	3.8[a] (4/4)	ND	ND
RSV 2B33F - 3b TS(+)	2B33F spinner passage, plaque picked at 39°C	0.5 (WT)	0.04	≤2.5[a] (3/4)	2.9[a] (4/4)	ND	ND
AGM pp2	2B33F-infected AGM #A2,d7 nasal wash plaque picked at 32°C	0.3 (ap,int)	0.00002	≤2.0[b] (1/4)	1.6[b] (4/4)	ND	ND

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Table 23 (continued)
RSV 2B, *ts* and Revertant Strains

Sample	Source	*In Vitro* Phenotype		*In Vivo* Growth*				
		ts	ca	Cotton Rat			AGM	
		39/32°C EOP plaque morph	20/32°C Yield	Nasal turbinates	Lungs	Nasal Wash	Bronchial Lavage
AGM pp4	2B33F-infected AGM #A2,d7 nasal wash plaque picked at 32°C	0.1 (ep.int)	0.008	<1.6[b] (0/4)	1.2[b] (4/4)	ND	ND
AGM pp6	2B33F-infected AGM #A4,d12 nasal wash plaque picked at 32°C	0.000004 (wt)	≤0.00005	≤1.5[b] (1/4)	<1.1[b] (0/4)	ND	ND
AGM pp7	2B33F-infected AGM #A4,d12 nasal wash plaque picked at 32°C	0.000004 (ep/int/wt)	0.007	≤1.4[b] (1/4)	<1.0[b] (0/4)	ND	ND
Chimp pp1A	2B33F-infected Chimp #1552, d4 tracheal lavage plaque picked at 32°C	0.5 (WT)	ND	ND	ND	ND	ND
Chimp pp3A	2B33F-infected Chimp #1560, d6 tracheal lavage plaque picked at 32°C	0.7 (WT)	ND	2.4[c] (4/4)	≤3.0[c] (3/4)	ND	ND
Chimp pp5A	2B33F-infected Chimp #1563, d10 nasal swab plaque picked at 32°C	0.7 (WT)	ND	≤2.3[c] (3/4)	3.0[c] (4/4)	ND	ND

Table 23 (continued)
RSV 2B, *ts* and Revertant Strains

Sample	Source	*In Vitro* Phenotype *ts*	*In Vitro* Phenotype ca	*In Vivo* Growth* Cotton Rat		AGM	
		39/32°C EOP plaque morph	20/32°C Yield	Nasal turbinates	Lungs	Nasal Wash	Bronchial Lavage
RSV 2B20L	ca, *ts* mutant isolated from 2B cold-passaged x 20	0.0002 (int/wt)	0.02	<1.9[d] (0/4)	<1.3[d] (0/4)	<0.7[f] (0/2)	<0.7[f] (0/2)
RSV 2B20L R1 TS(+)	2B20L spinner passage, plaque picked at 39°C	0.6 (WT)	ND	2.3[c] (4/4)	3.5[c] (4/4)	ND	ND
RSV 2B20L R2 TS(+)	2B20L spinner passage, plaque picked at 39°C	0.6 (WT)	ND	≤2.5[c] (3/4)	2.7[c] (4/4)	ND	ND
RSV 2B20L R9 TS(+)	2B20L spinner passage, plaque picked at 39°C	0.8 (WT)	ND	≤2.2[c] (3/4)	3.5[c] (4/4)	ND	ND
RSV 2B20L R10 TS(+)	2B20L spinner passage, plaque picked at 39°C	0.7 (WT)	ND	2.6[c] (4/4)	3.2[c] (4/4)	ND	ND

* *In Vivo* growth measured in $\log_{10}$ mean virus titer (# infected/# total)
ND = not done WT = wild-type plaque size sp = small plaque size int = intermediate plaque size

[a] Dose = $10^{6.7}$ PFU IN [b] Dose = $10^{5.6}$ PFU IN [c] Dose = $10^{6.3}$ PFU IN
[d] Dose = $10^{5.9}$ PFU IN [e] Dose = $10^{6.6}$ PFU IN+IT [f] Dose = $10^{6.0}$ PFU IN+IT

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Table 24

2B33F Revertants

	ts (+) *In vitro*			AGM				Chimp		
	5a	4a	3b	pp2	pp4	pp6	pp7	1A	3A	5A
base no.†										
M										
4176,4200	S	S	S	S	S	S	S	S	S	S
SH										
14 bases*	S	S	S	S	S	S	S	S	S	S
L										
9560	S	S	S	S	S	S	S	S	S	S
9854	2B	2B	2B	S	S	S	S	2B	2B	2B
12187	S	S	S	S	S	S	S	S	S	S
14588	S	S	S	S	S	S	S	S	S	S
15072	S	S	S	S	S	S	S	S	S	S
Phenotype										
ts	2B	2B	2B	r	r	S	S	2B	2B	2B
ca	S	S	S	2B	S	2B	S	ND	ND	ND
Attenuated	r	r	r	(r)	(r)	S	S	ND	r	r

† These 2B33F revertant base nos. are one larger than for 2B for M, SH and L genes

* bases 4330,4410,4421,4443,4455,4485,4498,4506,4526,4527,4543, 4562,4576,4599

S = same base as 2B33F

2B = reversion to 2B base or complete reversion in phenotype

r = moderate reversion in phenotype

(r) = slight reversion in phenotype

ND = not done

Table 25

2B20L Revertants

	TS(+) *In vitro* Isolates									
base no.†	R1	R2	R3A	R4A	R5A	R6A	R7A	R8A	R9A	R10A
L										
8964	S	S	S	S	S	S	S	S	S	S
13348	C*	S	ND	S	S	ND	S	S	S	S
14588	S	S	S	S	S	S	S	S	S	S
14650	S	S	2B	S	2B	2B	S	S	2B	2B
14651	A*	A*	S	A*	S	S	A*	A*	S	S
Phenotype										
ts	2B	2B	ND	ND	ND	ND	ND	ND	2B	2B
Attenuated	r	r	ND	ND	ND	ND	ND	ND	r	r

† These 2B20L revertant base nos. are one larger than for 2B for L genes

S = same base as 2B20L

2B = reversion to 2B base

r = moderate reversion in phenotype

* = base change, different from 2B or 2B20L

ND = not done

Table 26
RSV 2B, *ts* and Revertant Strains: Phenotype Summary

Virus Isolate	Source	*In Vitro* Phenotype *ts*	*ca*	*In Vivo* Attenuation Cotton Rat	AGM
RSV 2B	Wild-type Parent Strain	-	-	-	-
RSV 2B33F	ca, *ts* mutant isolated from 2B, cold-passaged x 33	++++	++	++++	+++
RSV 2B33F - 5a TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	+
RSV 2B33F - 4a TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	ND
RSV 2B33F - 3b TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	ND
AGM pp2	2B33F-infected AGM A2, d7 nasal wash plaque picked at 32°C	+	-	+++	ND
AGM pp4	2B33F-infected AGM A2, d7 nasal wash plaque picked at 32°C	+	++	+++	ND
AGM pp6	2B33F-infected AGM A4, d12 nasal wash plaque picked at 32°C	++++	-	++++	ND
AGM pp7	2B33F-infected AGM A4, d12 nasal wash plaque picked at 32°C	++++	++	++++	ND
Chimp pp1A	2B33F-infected chimp #1552, d4 tracheal lavage, plaque picked at 32°C	-	ND	ND	ND
Chimp pp3A	2B33F-infected chimp #1560, d6 tracheal lavage, plaque picked at 32°C	-	ND	++	ND
Chimp pp5A	2B33F-infected chimp #1563, d10 tracheal lavage, plaque picked at 32°C	-	ND	++	ND

Table 26 (continued)
RSV 2B, *ts* and Revertant Strains: Phenotype Summary

Virus Isolate	Source	*In Vitro* Phenotype		*In Vivo* Attenuation	
		ts	ca	Cotton Rat	AGM
RSV 2B20L	ca, *ts* mutant isolated from 2B, cold-passaged x 20	++++	++	++++	++++
RSV 2B20L R1 TS(+)	2B20L spinner passage plaque picked at 39°C	-	ND	++	ND
RSV 2B20L R2 TS(+)	2B20L spinner passage plaque picked at 39°C	-	ND	++	ND
RSV 2B20L R9 TS(+)	2B20L spinner passage plaque picked at 39°C	-	ND	++	ND
RSV 2B20L R10 TS(+)	2B20L spinner passage plaque picked at 39°C	-	ND	++	ND

ND = not done

- = wild-type phenotype, i.e., not temperature sensitive, not cold-adapted, not attenuated

+ to ++++ = increasing levels of temperature sensitivity, cold-adaptation or attenuation

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09508915.051699

What is claimed is:

1. An isolated, recombinantly-generated, attenuated, human respiratory syncytial virus (RSV) subgroup B having at least one attenuating mutation in the RNA polymerase gene.

2. The virus of Claim 1 wherein the at least one attenuating mutation in the RNA polymerase gene is selected from the group consisting of nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid).

3. A vaccine comprising an isolated, recombinantly-generated, attenuated RSV subgroup B according to Claim 1 and a physiologically acceptable carrier.

4. A vaccine comprising an isolated, recombinantly-generated, attenuated RSV subgroup B according to Claim 2 and a physiologically acceptable carrier.

5. A method for immunizing an individual to induce protection against RSV subgroup B which comprises administering to the individual the vaccine of Claim 3.

6. A method for immunizing an individual to induce protection against RSV subgroup B which comprises administering to the individual the vaccine of Claim 4.

7. A composition which comprises a trancription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of an RSV subgroup B having at least one attenuating mutation in

the RNA polymerase gene, together with at least one expression vector which comprises at least one isolated nucleic acid molecule encoding the trans-acting N, P, L and M2 proteins of the virus necessary for encapsidation, transcription and replication, whereby upon expression an infectious attenuated virus is produced.

8. The composition of Claim 7 wherein the transcription vector comprises an isolated nucleic acid molecule which encodes an RSV subgroup B according to Claim 2.

9. A method for producing infectious attenuated RSV subgoup B which comprises transforming or transfecting host cells with the at least two vectors of Claim 7 and culturing the host cells under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated virus.

10. The method of Claim 9 wherein the virus is the RSV subgroup B of Claim 2.

11. An isolated nucleic acid molecule comprising a RSV subgroup B sequence in positive strand, antigenomic message sense selected from the group consisting of 2B wild-type strain (SEQ ID NO:1), 18537 wild-type strain (SEQ ID NO:3), 2B33F vaccine strain (SEQ ID NO:5), 2B20L vaccine strain (SEQ ID NO:7), 2B33F TS(+) revertant strain (SEQ ID NO:9), and 2B20L TS(+) revertant strain (SEQ ID NO:11), and the complementary genomic sequences thereof.

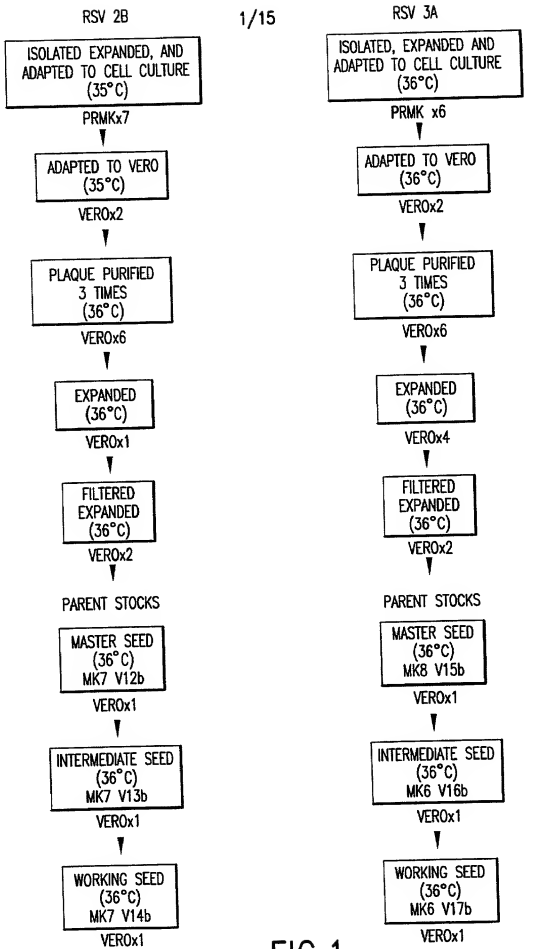
RSV 2B
ISOLATED EXPANDED, AND ADAPTED TO CELL CULTURE (35°C)
PRMKx7
ADAPTED TO VERO (35°C)
VEROx2
PLAQUE PURIFIED 3 TIMES (36°C)
VEROx6
EXPANDED (36°C)
VEROx1
FILTERED EXPANDED (36°C)
VEROx2
PARENT STOCKS
MASTER SEED (36°C) MK7 V12b
VEROx1
INTERMEDIATE SEED (36°C) MK7 V13b
VEROx1
WORKING SEED (36°C) MK7 V14b
VEROx1
RSV 3A
ISOLATED, EXPANDED AND ADAPTED TO CELL CULTURE (36°C)
PRMK x6
ADAPTED TO VERO (36°C)
VEROx2
PLAQUE PURIFIED 3 TIMES (36°C)
VEROx6
EXPANDED (36°C)
VEROx4
FILTERED EXPANDED (36°C)
VEROx2
PARENT STOCKS
MASTER SEED (36°C) MK8 V15b
VEROx1
INTERMEDIATE SEED (36°C) MK6 V16b
VEROx1
WORKING SEED (36°C) MK6 V17b
VEROx1

FIG.1

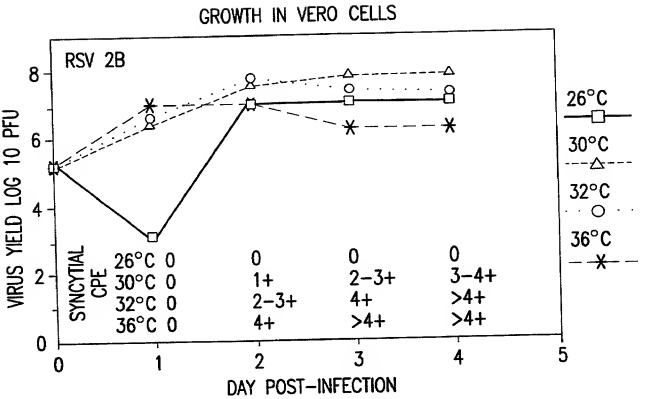
GROWTH IN VERO CELLS
RSV 2B
VIRUS YIELD LOG 10 PFU
DAY POST-INFECTION
SYNCYTIAL CPE
26°C 0 0 0 0
30°C 0 1+ 2-3+ 3-4+
32°C 0 2-3+ 4+ >4+
36°C 0 4+ >4+ >4+
26°C
30°C
32°C
36°C

FIG.2

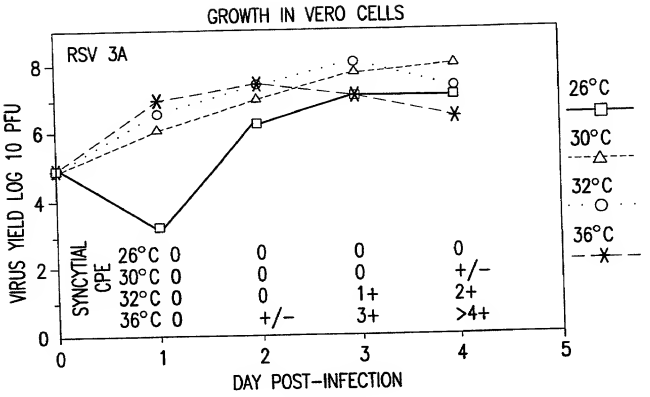
GROWTH IN VERO CELLS
RSV 3A
VIRUS YIELD LOG 10 PFU
DAY POST-INFECTION
SYNCYTIAL CPE
26°C 0 0 0 0
30°C 0 0 0 +/-
32°C 0 0 1+ 2+
36°C 0 +/- 3+ >4+
26°C
30°C
32°C
36°C

FIG.3

FIG.4A

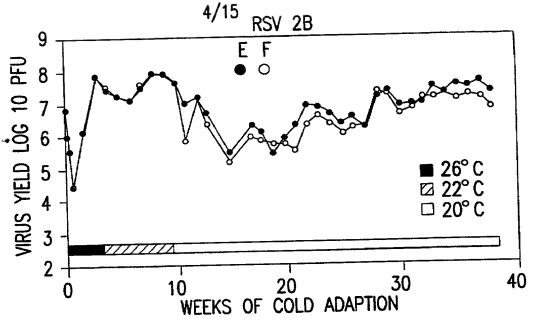

FIG.4B

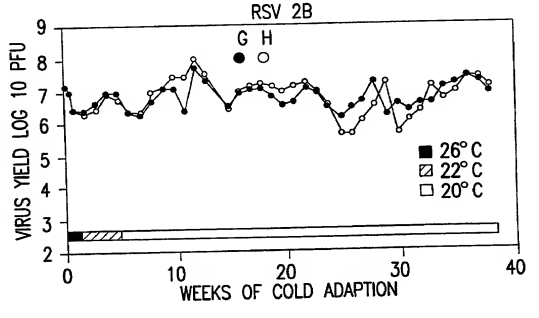

FIG.4C

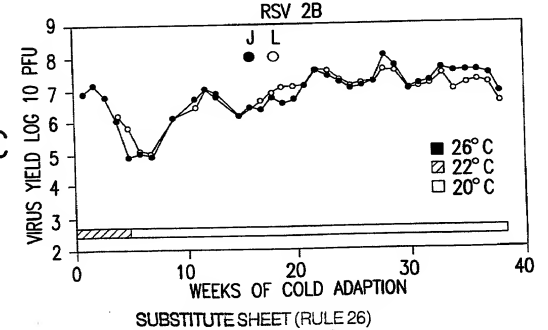

FIG.4D

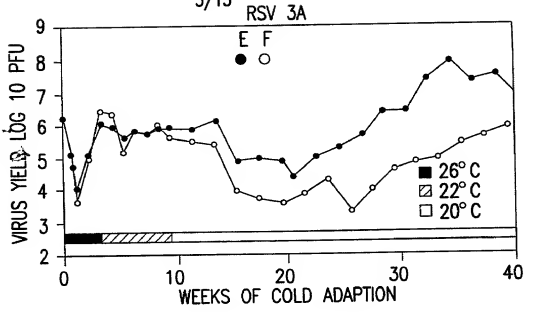

FIG.4E

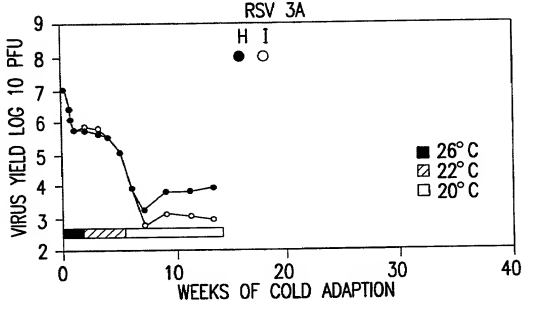

FIG.4F

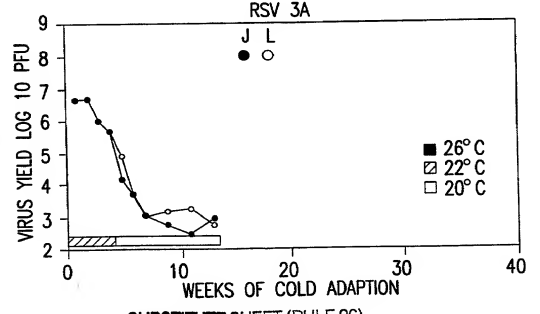

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FIG.5A

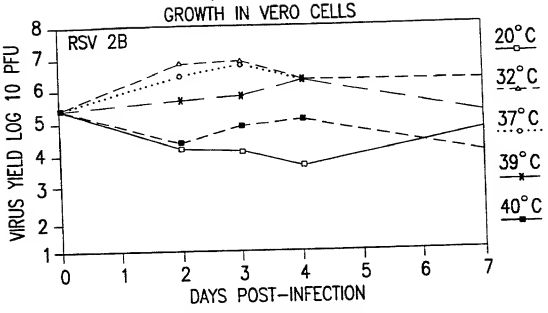


FIG.5B

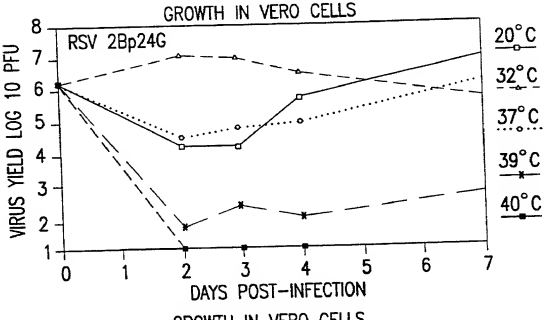


FIG.5C

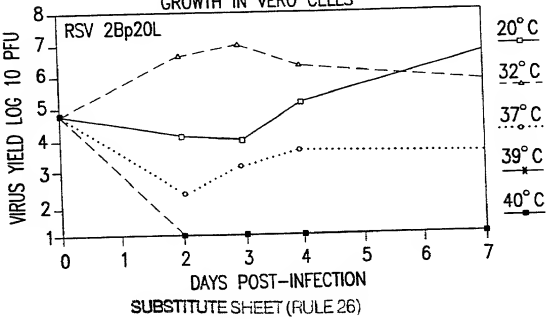


FIG.5D

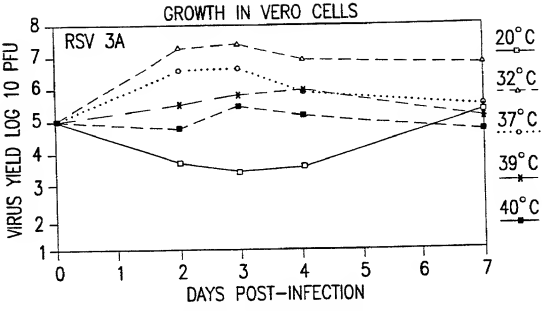


FIG.5E

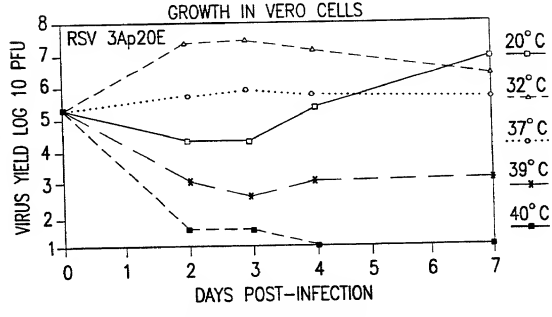
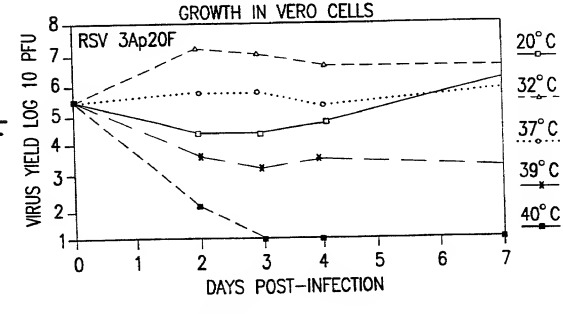
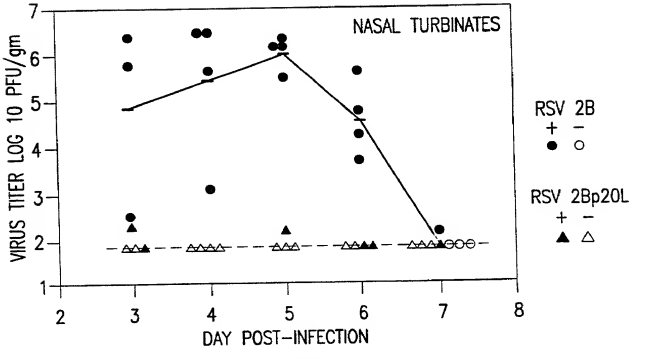


FIG.5F

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VIRUS TITER LOG 10 PFU/gm
DAY POST-INFECTION
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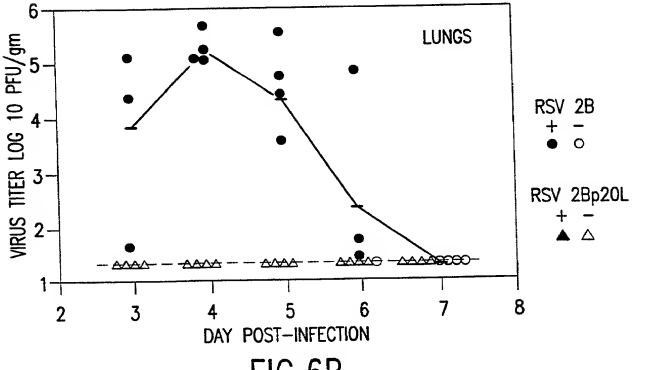
+ −
RSV 2Bp20L
+ −

FIG.6A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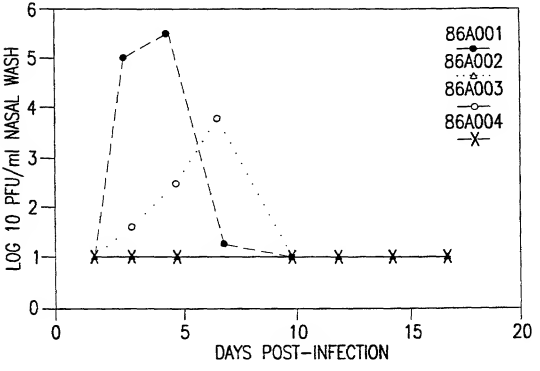
RSV 2Bp20L
+ −

FIG.6B



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COUGH	0	0	0	0	0	0	0	2	1	0	1	1	1	0	1	1	1	0	0	0	0
86A004 RSV 2B 5.0 PFU																					
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COUGH	0	0	0	0	0	0	0	0	0	0	1	2	2	1	1	1	1	1	0	0	0
86A001 RSV 2Bp20L 4.0 PFU																					
NASAL DISCHARGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COUGH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86A002 RSV 2Bp20L 5.0 PFU																					
NASAL DISCHARGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
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FIG.7

FIG.8A

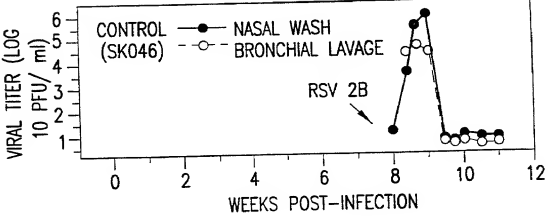


FIG.8B

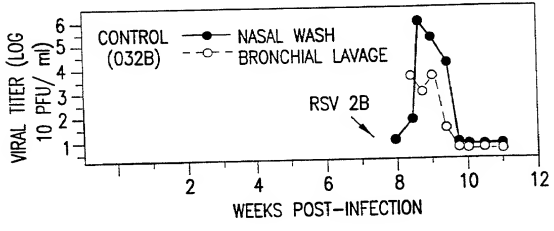


FIG.8C

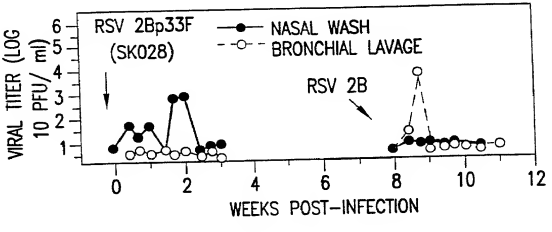


FIG.8D

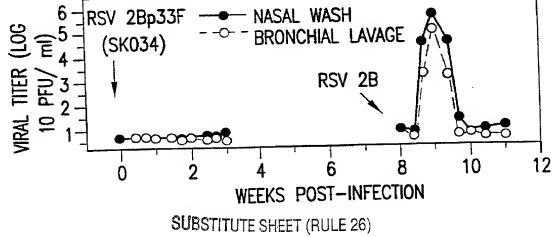


FIG.8E

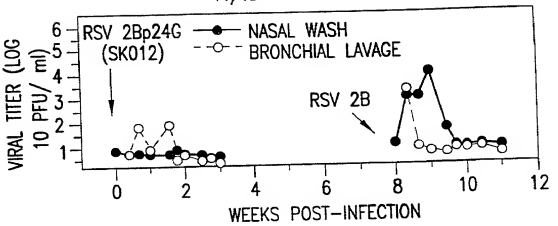


FIG.8F

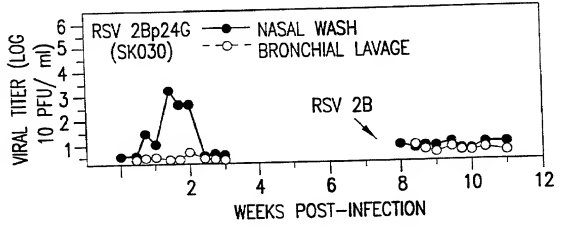


FIG.8G

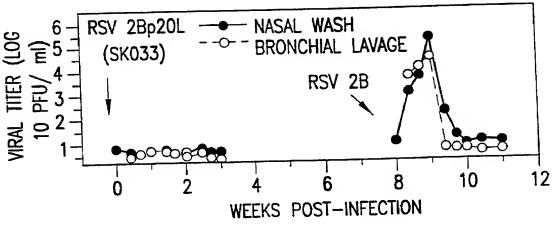


FIG.8H

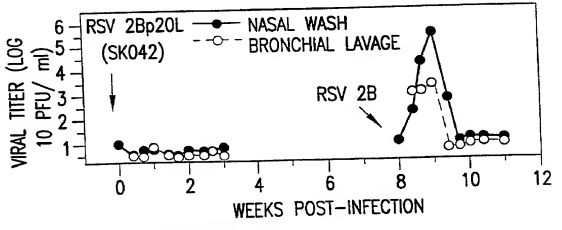


FIG.9A

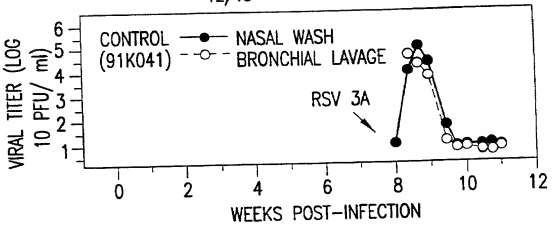


FIG.9B

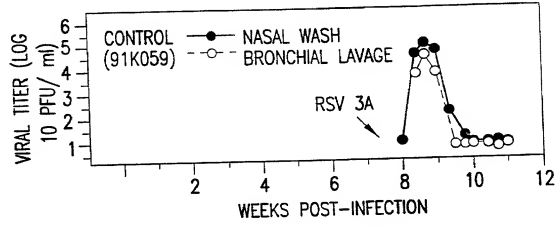


FIG.9C

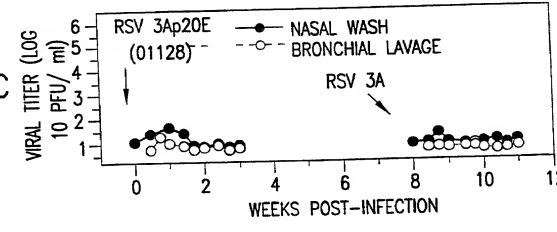


FIG.9D

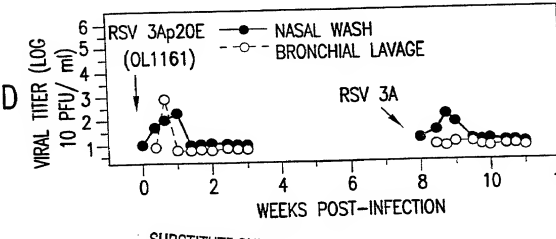


FIG.9E

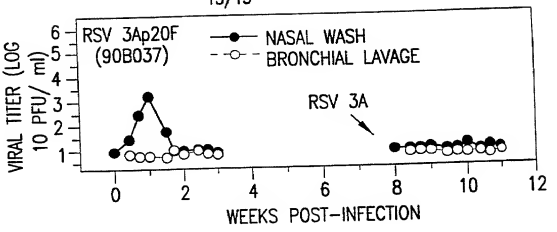


FIG.9F

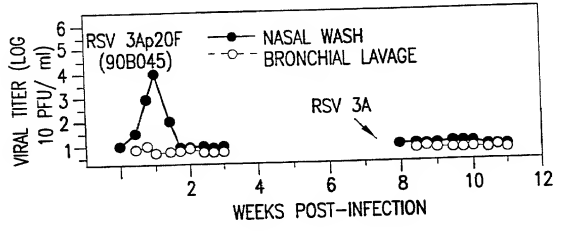


FIG.9G

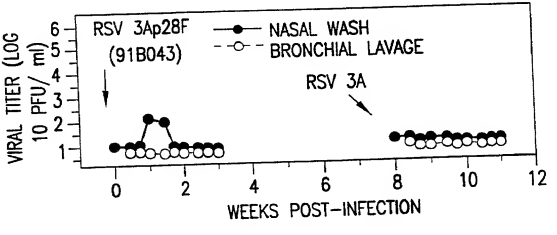


FIG.9H

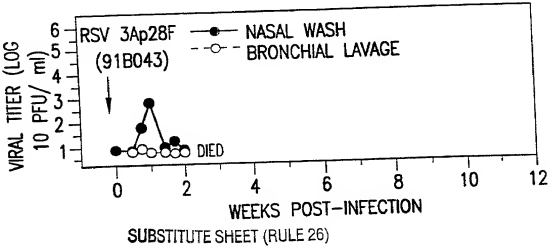


FIG.10A

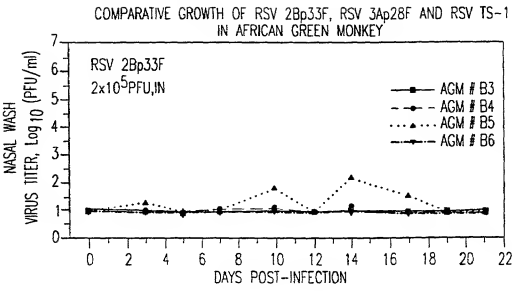


FIG.10B

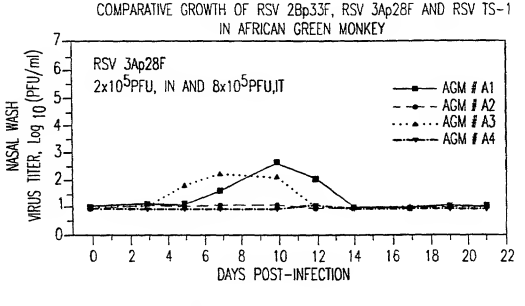
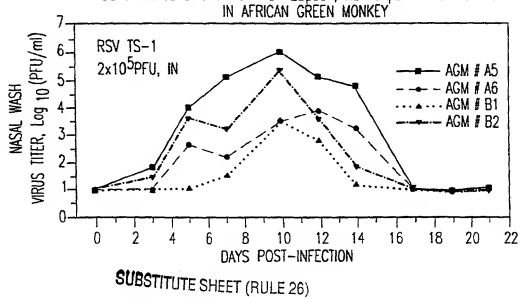


FIG.10C



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18537 44 532 503 1202 914 956 413 926 1901 960 6580 149
GENE-END INTER GENIC GENE-START
NS-1/NS-2
NS-2/N
N/P AUG (3)
P/M CUGUUCUA (9)
M/SH GGUUUUAU (9)
SH/G (44)
G/F (52)
F/M2 (56)
2B 18537
2B 18537
TOTAL LENGTH
2B = 15,218
18537 = 15,229
M2 GENE
L GENE
3' AUUCCAAUA
L GENE-START
68 NUCLEOTIDE OVERLAP
M2 GENE-END
5'

FIG.11

COMBINED DECLARATION AND POWER OF ATTORNEY
(Original, Design, Supplemental, Divisional, Continuation, CIP)

As the below named inventor, I hereby declare that:

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

ATTENUATED RESPIRATORY SYNCYTIAL VIRUSES

SPECIFICATION IDENTIFICATION

the specification of which: (complete (a), (b), or (c))

(a) ☐ is attached hereto.

(b) ☐ was filed on as
- ☐ Serial Number
- ☐ Express Mail No. , as Serial Number not yet known

(c) ☒ was described and claimed in PCT International Application No. PCT/US98/19145 filed on September 15, 1998 and as amended under PCT Article 19 on (if any).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37 CFR 1.56(a).

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventors certificate or of any PCT International application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate of any PCT International application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(d) ☒ No such applications have been filed.
(e) ☐ Such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority, check item (e), enter the details below and make the priority claim.

Earliest Foreign Application(s), if any, filed within 12 months (6 months for Design) prior to this U.S. Application

Country	Application No.	Date of Filing (Day, Month, Year)	Priority Claimed 35 USC 119

All Foreign Application(s), if any, Filed More Than 12 Months (6 Months for Design) Prior to This U.S. Application)

09876543210987

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. § 119(E))

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	**FILING DATE**
60/059,552	September 19, 1997

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)
(UNDER 35 U.S.C. 120)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT International filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 USC 120

U.S. Applications		**Status (Check One)**		
U.S. Applications	U.S. Filing Date	Patented	Pending	Abandoned
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐

PCT Applications Designating U.S.		
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NO. ASSIGNED (if any)
PCT/US98/19145	9/15/98	

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Elizabeth M. Barnhard, Reg. No. 31,088; Rebecca R. Barrett, Reg. No. ~~35,152~~; Egon E. Berg, Reg. No. 21,~~117~~; William H. Calnan, Reg. No. 29,520; Milagros A. Cepeda, Reg. No. 33,365; Charles F. Costello, Jr., Reg. No. 27,324; Steven R. Eck, Reg. No. ~~36,126~~; Bruce M. Eisen, Reg. No. 22,~~847~~; Steven H. Flynn, Reg. No. 29,639; Alan M. Gordon, Reg. No. 30,~~637~~; Barbara A. Gyure, Reg. No. 34,614; John W. Hogan, Jr., Reg. No. 32,703; Patrick J. Igoe, Reg. No. 35,202; Adley F. Mandel, Reg. No. 26,942; Gale F. Matthews, Reg. No. 32,~~269~~; Joseph M. Mazzarese, Reg. No. 32,~~803~~; Arnold S. Milowsky, Reg. No. 35,288; Daniel B. Moran, Reg. No. 41,204; Michael R. Nagy, Reg. No. 33,432; Barbara L. Renda, Reg. No. ~~27,626~~; George Tarnowski, Reg. No. 27,472; and Darryl L. Webster, Reg. No. 34,276 all of AMERICAN HOME PRODUCTS CORPORATION, One Campus Drive, Parsippany, New Jersey 07054.

☐ Attached as part of this declaration and power of attorney is the authorization of the above-named attorney(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE AND TELEPHONE CALLS TO:

~~Alan M. Gordon~~
~~American Home Products Corporation~~
~~Patent Law Department~~
~~One Campus Drive~~
~~Parsippany, NJ 07054~~
Tel. No. (973) 683-2157

DECLARATION

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full name of SOLE OR FIRST INVENTOR: **Stephen A. Udem**

Inventor's Signature: _____ Date: March 7, 2000

Country of Citizenship: **United States of America**
Residence: **155 West 70th Street, Apt. 6F/G, New York, New York 10023** NY
Post Office Address: **155 West 70th Street, Apt. F/G, New York, New York 10023**

Full name of SECOND JOINT INVENTOR: **Mohinderjit S. Sidhu**

Inventor's Signature: _____ Date: 3/8/00

Country of Citizenship: **United States of America**
Residence: **35 Lowell Drive, New City, New York 10956** NY
Post Office Address: **35 Lowell Drive, New City, New York 10956**

Full name of THIRD JOINT INVENTOR: **Valerie B. Randolph**

Inventor's Signature: _____ Date: March 7, 2000

Country of Citizenship: **United States of America**
Residence: **535 Pine Brook Road, Lincoln Park, New Jersey 07035** NJ
Post Office Address: **535 Pine Brook Road, Lincoln Park, New Jersey 07035**

Full name of FOURTH JOINT INVENTOR:

Inventor's Signature: _____ Date: March 7, 2000

Country of Citizenship:
Residence:
Post Office Address:

SEQUENCE LISTING

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Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Ser
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His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190

Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205

Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220

Glu Val Lys Ser His Gly Phe Ile Leu Ile Asp Asn Gln Thr Leu Ser
225                 230                 235                 240

Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255

Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270
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Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
275 280 285

Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
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Phe Asn Asn Val Val Leu Ser Gln Leu Phe Leu Tyr Gly Asp Cys Ile
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Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
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Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
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Arg Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
355 360 365

Ile Lys Ala Gln Lys Asp Leu Leu Ser Arg Val Cys His Thr Leu Leu
370 375 380

Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
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Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
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Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
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Met Val Asp Glu Arg Gln Ala Met Asp Ser Val Arg Ile Asn Cys Asn
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Glu Thr Lys Phe Tyr Leu Leu Ser Ser Leu Ser Thr Leu Arg Gly Ala
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Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Thr Tyr Asn Arg Trp
465 470 475 480

Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Asn Tyr
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Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Ile Thr Glu Asn Asp
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Leu Ile Ile Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe His Leu Pro
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Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
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Pro Lys Asp Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560

His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575

Asp Arg Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590

Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605

Asn Ser Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620

Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Ile Gln
625                 630                 635                 640

Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655

Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
            660                 665                 670

Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
        675                 680                 685

Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
    690                 695                 700

Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                 710                 715                 720

Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                 730                 735

Ile Pro Leu Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Phe
            740                 745                 750

Ile Lys Asp His Val Val Asn Leu Asn Glu Val Asp Glu Gln Ser Gly
        755                 760                 765

Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
    770                 775                 780
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SUBSTITUTE SHEET (RULE 26)

Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785 790 795 800

Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
805 810 815

Ile Ser Lys Pro Val Arg Leu Ile Glu Gly Gln Thr His Ala Gln Ala
820 825 830

Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
835 840 845

Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
850 855 860

Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
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Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
885 890 895

Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
900 905 910

Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
915 920 925

Arg Asn Ile Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Arg Asn His
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Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
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His Leu Lys Thr Phe Phe Asn Leu Asp Ser Ile Asp Met Ala Leu Ser
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Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
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Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
995 1000 1005

Ile Val His Ser Val Phe Val Leu Ser Tyr Tyr Thr Gly His Asp Leu
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Gln Asp Lys Leu Gln Asp Leu Pro Asp Asp Arg Leu Asn Lys Phe Leu
1025 1030 1035 1040

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Thr Cys Val Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
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Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
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Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Ile Ala
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Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
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Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
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Gly Leu Arg Val Val Tyr Glu Ser Leu Pro Phe Tyr Lys Ala Glu Lys
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Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
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Lys Thr Ser Ala Ile Asp Thr Thr Asp Ile Asn Arg Ala Thr Asp Met
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Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
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Asn Lys Asp Lys Arg Glu Leu Leu Ser Leu Glu Asn Leu Ser Ile Thr
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Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
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Val Gly Val Thr Ser Pro Ser Ile Met Phe Thr Met Asp Ile Lys Tyr
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Thr Thr Ser Thr Ile Ala Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
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Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly
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Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
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Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
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Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
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Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
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Tyr His Phe Asp Thr Ser Pro Ile Asn His Val Leu Thr Glu Lys Tyr
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Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
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Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Ile Cys Pro Asn
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Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
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Pro Ile Phe Thr Gly Asp Val Asp Ile Ile Lys Leu Lys Gln Val Ile
1425                1430                1435                1440

Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
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Val Glu Leu Phe Leu Ser Asn Lys Ala Leu Lys Ser Gly Ser His Ile
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Asn Ser Asn Leu Ile Leu Val His Lys Met Ser Asp Tyr Phe His Asn
       1475                1480                1485

Ala Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
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Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
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Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Asn Val Phe Phe Asn
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Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
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Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
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Gln Lys Val Ile Lys Tyr Ile Val Asn Gln Asp Thr Ser Leu Arg Arg
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Ile Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
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Asn Ala Lys Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
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Pro Thr His Met Lys Ala Ile Leu Ser Tyr Ile Asp Leu Val Arg Met
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Gly Leu Ile Asn Val Asp Lys Leu Thr Ile Lys Asn Lys Asn Lys Phe
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Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Ser Tyr Asn Phe
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Ser Asp Asn Thr His Leu Leu Thr Lys Gln Ile Arg Ile Ala Asn Ser
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Glu Leu Glu Asp Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
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Pro Lys Phe Cys Ile Ser Gly Asn Thr Glu Ser Met Met Met Ser Thr
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Phe Ser Ser Lys Met His Ile Lys Ser Ser Thr Val Thr Thr Arg Phe
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Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Ile Val Val Ile
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Asp Lys Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
1780 1785 1790

Tyr Thr Thr Thr Ser His Gln Thr Ser Leu Val Arg Asn Ser Ala Ser
1795 1800 1805

Leu Tyr Cys Met Leu Pro Trp His His Val Asn Arg Phe Asn Phe Val
1810 1815 1820

Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825 1830 1835 1840

Leu Lys Ile Lys Asp Pro Ser Cys Ile Ala Phe Ile Gly Glu Gly Ala
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Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
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1890 1895 1900

Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
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Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Ile Phe Val Cys Asp
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Ala Glu Leu Pro Val Thr Ala Asn Trp Ser Lys Ile Ile Ile Glu Trp
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Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Arg Cys
1955 1960 1965

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2005 2010 2015

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2020 2025 2030

Thr Lys Asn Phe Ile Met Pro Lys Lys Thr Asp Lys Glu Ser Ile Asp
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Ala Asn Ile Lys Ser Leu Ile Pro Phe Leu Cys Tyr Pro Ile Thr Lys
2050 2055 2060

Lys Gly Ile Lys Thr Ser Leu Ser Lys Leu Lys Ser Val Val Asn Gly
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Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
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SUBSTITUTE SHEET (RULE 26)

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Ser Tyr Leu Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35                  40                  45

Ile Ser Arg Gln Ser Pro Leu Leu Glu His Met Asn Leu Lys Lys Leu
    50                  55                  60

Thr Ile Thr Gln Ser Leu Ile Ser Arg Tyr His Lys Gly Glu Leu Lys
65                  70                  75                  80

Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
                85                  90                  95

Met Ser Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
            100                 105                 110

Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
        115                 120                 125

Asn Lys Leu Gly Leu Lys Glu Lys Asp Arg Val Lys Pro Asn Asn Asn
    130                 135                 140

Ser Gly Asp Glu Asn Ser Val Leu Thr Thr Ile Ile Lys Asp Asp Ile
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Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Asn
                165                 170                 175

His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190

Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205

Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220

Glu Val Lys Ser His Gly Phe Ile Leu Ile Asp Asn Gln Thr Leu Ser
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Asp Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255
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Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270

Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285

Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300

Phe Asn Asn Val Val Leu Ser Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320

Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
                325                 330                 335

Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
            340                 345                 350

Arg Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
        355                 360                 365

Ile Lys Ala Gln Lys Asn Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380

Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
385                 390                 395                 400

Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
                405                 410                 415

Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
            420                 425                 430

Met Val Asp Glu Arg Gln Ala Met Asp Ala Val Arg Ile Asn Cys Asn
        435                 440                 445

Glu Thr Lys Phe Tyr Leu Leu Ser Asn Leu Ser Thr Leu Arg Gly Ala
    450                 455                 460

Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Thr Tyr Asn Arg Trp
465                 470                 475                 480

Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Asn Tyr
                485                 490                 495

Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Ile Thr Glu Lys Asp
            500                 505                 510
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Leu Ile Ile Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe His Leu Pro
        515                 520                 525

Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540

Pro Lys Asp Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560

His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575

Asp Arg Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590

Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605

Asn Ser Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620

Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Ile Gln
625                 630                 635                 640

Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655

Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
            660                 665                 670

Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
        675                 680                 685

Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
    690                 695                 700

Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                 710                 715                 720

Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                 730                 735

Ile Pro Leu Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Phe
            740                 745                 750

Ile Lys Asp His Val Val Asn Leu Asn Lys Val Asp Glu Gln Ser Gly
        755                 760                 765
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Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
    770                 775                 780

Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785                 790                 795                 800

Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
                805                 810                 815

Ile Ser Lys Pro Val Arg Leu Ile Glu Gly Gln Thr His Ala Gln Ala
            820                 825                 830

Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
        835                 840                 845

Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
    850                 855                 860

Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865                 870                 875                 880

Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
                885                 890                 895

Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
            900                 905                 910

Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
        915                 920                 925

Arg Asn Ile Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Arg Asn His
    930                 935                 940

Ala Leu Cys His Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945                 950                 955                 960

His Leu Lys Thr Phe Phe Asn Leu Asp Ser Ile Asp Met Ala Leu Thr
                965                 970                 975

Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
            980                 985                 990

Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
        995                 1000                1005

Ile Val His Ser Val Phe Val Leu Ser Tyr Tyr Thr Gly His Asp Leu
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Thr Cys Ile Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
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Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
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Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Ile Ala
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Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
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Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
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Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
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Val Gly Val Thr Ser Pro Ser Ile Met Phe Thr Met Asp Ile Lys Tyr
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Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
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Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
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Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
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Ser Thr Gly Thr Leu Gly Leu Ser Tyr Glu Lys Ala Lys Lys Leu Phe
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Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
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Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
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Tyr His Phe Asp Thr Ser Pro Ile Asn His Val Leu Thr Glu Lys Tyr
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Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
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Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Ile Cys Pro Asn
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Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
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Pro Ile Phe Thr Gly Asp Val Asp Ile Ile Lys Leu Lys Gln Val Ile
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Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
                1445                1450                1455

Val Glu Leu Phe Leu Ser Asn Lys Ala Leu Lys Ser Gly Ser His Ile
            1460                1465                1470

Asn Ser Asn Leu Ile Leu Val His Lys Met Ser Asp Tyr Phe His Asn
        1475                1480                1485

Ala Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
    1490                1495                1500

Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
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Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Asn Val Phe Phe Asn
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Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
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Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
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Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
   1570                1575                1580

Gln Lys Val Ile Lys Tyr Ile Ile Asn Gln Asp Thr Ser Leu His Arg
1585                1590                1595                1600

Ile Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
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Asn Ala Lys Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
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Pro Thr His Met Lys Ala Ile Leu Ser Tyr Ile Asp Leu Val Arg Met
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Gly Leu Ile Asn Val Asp Lys Leu Thr Ile Lys Asn Lys Asn Lys Phe
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Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Ser Tyr Asn Phe
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Ser Asp Asn Thr His Leu Leu Thr Lys Gln Ile Arg Ile Ala Asn Ser
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Glu Leu Glu Asn Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
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Leu Glu Asn Met Ser Leu Ile Pro Val Lys Ser Asn Asn Ser Asn Lys
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Pro Lys Phe Gly Ile Ser Gly Asn Thr Glu Ser Met Met Thr Ser Thr
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Phe Ser Asn Lys Thr His Ile Lys Ser Ser Ala Val Ile Thr Arg Phe
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Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Ile Val Val Ile
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Asp Arg Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
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Tyr Thr Thr Thr Ser His Gln Thr Ser Leu Val Arg Asn Ser Ala Ser
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Leu Tyr Cys Met Leu Pro Trp His His Val Asn Arg Phe Asn Phe Val
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Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
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Leu Lys Ile Lys Asp Pro Ser Cys Ile Ala Phe Ile Gly Glu Gly Ala
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Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
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Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
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Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
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Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Ile Phe Val Cys Asp
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Ala Glu Leu Pro Val Thr Ala Asn Trp Ser Lys Ile Ile Ile Glu Trp
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Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Arg Cys
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Ile Leu Ile Ala Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
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Asp Asn Ile Thr Ile Leu Lys Thr Tyr Val Cys Leu Gly Ser Lys Leu
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Lys Gly Ser Glu Val Tyr Leu Val Leu Thr Ile Gly Pro Ala Asn Ile
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Leu Pro Val Phe Asn Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
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Ser Tyr Leu Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35                  40                  45

Ile Ser Arg Gln Ser Pro Leu Leu Glu His Met Asn Leu Lys Lys Leu
    50                  55                  60

Thr Ile Thr Gln Ser Leu Ile Ser Arg Tyr His Lys Gly Glu Leu Lys
65                  70                  75                  80

Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
                85                  90                  95

Met Ser Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
            100                 105                 110

Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
        115                 120                 125

Asn Lys Leu Gly Leu Lys Glu Lys Asp Arg Val Lys Pro Asn Asn Asn
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Ser Gly Asp Glu Asn Ser Val Leu Thr Thr Ile Ile Lys Asp Asp Ile
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Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Ser
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His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190

Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205

Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
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Glu Val Lys Ser His Gly Phe Ile Leu Ile Asp Asn Gln Thr Leu Ser
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Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
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Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270

Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285

Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300

Phe Asn Asn Val Val Leu Ser Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320

Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
                325                 330                 335

Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
            340                 345                 350

Lys Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
        355                 360                 365

Ile Lys Ala Gln Lys Asp Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380

Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
385                 390                 395                 400

Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
                405                 410                 415

Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
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Met Val Asp Glu Arg Gln Ala Met Asp Ser Val Arg Ile Asn Cys Asn
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Glu Thr Arg Phe Tyr Leu Leu Ser Ser Leu Ser Thr Leu Arg Gly Ala
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Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Thr Tyr Asn Arg Trp
465                 470                 475                 480

Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Asn Tyr
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SUBSTITUTE SHEET (RULE 26)

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Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Ile Thr Glu Asn Asp
            500                 505                 510

Leu Ile Ile Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe His Leu Pro
        515                 520                 525

Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540

Pro Lys Asp Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560

His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575

Asp Arg Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590

Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605

Asn Ser Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620

Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Ile Gln
625                 630                 635                 640

Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655

Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
            660                 665                 670

Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
        675                 680                 685

Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
    690                 695                 700

Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                 710                 715                 720

Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                 730                 735

Ile Pro Leu Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Phe
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SUBSTITUTE SHEET (RULE 26)

WO 9915672A1

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Ile Lys Asp His Val Val Asn Leu Asn Glu Val Asp Glu Gln Ser Gly
        755                 760                 765

Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
    770                 775                 780

Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785                 790                 795                 800

Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
                805                 810                 815

Ile Ser Lys Pro Val Arg Leu Ile Glu Gly Gln Thr His Ala Gln Ala
            820                 825                 830

Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
        835                 840                 845

Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
    850                 855                 860

Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865                 870                 875                 880

Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
                885                 890                 895

Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
            900                 905                 910

Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
        915                 920                 925

Arg Asn Ile Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Arg Asn His
    930                 935                 940

Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945                 950                 955                 960

His Leu Lys Thr Phe Phe Asn Leu Asp Ser Ile Asp Met Ala Leu Ser
                965                 970                 975

Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
            980                 985                 990

Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
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995 1000 1005

Ile Val His Ser Val Phe Val Leu Ser Tyr Tyr Thr Gly His Asp Leu
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Gln Asp Lys Leu Gln Asp Leu Pro Asp Asp Arg Leu Asn Lys Phe Leu
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Thr Cys Val Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
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Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
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Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Ile Ala
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Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
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Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
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1125 1130 1135

Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
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Lys Thr Ser Ala Ile Asp Thr Thr Asp Ile Asn Arg Ala Thr Asp Met
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Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
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Asn Lys Asp Lys Arg Glu Leu Leu Ser Leu Glu Asn Leu Ser Ile Thr
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Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
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Val Gly Val Thr Ser Pro Ser Ile Met Phe Thr Met Asn Ile Lys Tyr
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Thr Thr Ser Thr Ile Ala Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
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Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly

1250 1255 1260

Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
1265 1270 1275 1280

Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
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Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
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Ser Thr Gly Thr Leu Gly Leu Ser Tyr Glu Lys Ala Lys Lys Leu Phe
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Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
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Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
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Tyr His Phe Asp Thr Ser Pro Ile Asn His Val Leu Thr Glu Lys Tyr
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Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
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Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Ile Cys Pro Asn
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Pro Ile Phe Thr Gly Asp Val Asp Ile Ile Lys Leu Lys Gln Val Ile
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Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
1445 1450 1455

Val Glu Leu Phe Leu Ser Asn Lys Ala Leu Lys Ser Gly Ser His Ile
1460 1465 1470

Asn Ser Asn Leu Ile Leu Val His Lys Met Ser Asp Tyr Phe His Asn
1475 1480 1485

Ala Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
1490 1495 1500

Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu

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Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Asn Val Phe Phe Asn
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Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
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Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
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Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
1570 1575 1580

Gln Lys Val Ile Lys Tyr Ile Val Asn Gln Asp Thr Ser Leu Arg Arg
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Ile Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
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Pro Thr His Met Lys Ala Ile Leu Ser Tyr Ile Asp Leu Val Arg Met
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Ser Asp Asn Thr His Leu Leu Thr Lys Gln Ile Arg Ile Ala Asn Ser
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Glu Leu Glu Asp Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
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Pro Lys Phe Cys Ile Ser Gly Asn Thr Glu Ser Met Met Met Ser Thr
1730 1735 1740

Phe Ser Ser Lys Met His Ile Lys Ser Ser Thr Val Thr Thr Arg Phe
1745 1750 1755 1760

Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Ile Val Val Ile

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Asp Lys Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
            1780                1785                1790

Tyr Thr Thr Thr Ser His Gln Thr Ser Leu Val Arg Asn Ser Ala Ser
        1795                1800                1805

Leu Tyr Cys Met Leu Pro Trp His His Val Asn Arg Phe Asn Phe Val
    1810                1815                1820

Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825                1830                1835                1840

Leu Lys Ile Lys Asp Pro Ser Cys Ile Ala Phe Ile Gly Glu Gly Ala
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Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
            1860                1865                1870

Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
        1875                1880                1885

Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
    1890                1895                1900

Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
1905                1910                1915                1920

Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Ile Phe Val Cys Asp
                1925                1930                1935

Ala Glu Leu Pro Val Thr Ala Asn Trp Ser Lys Ile Ile Ile Glu Trp
            1940                1945                1950

Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Arg Cys
        1955                1960                1965

Ile Leu Ile Ala Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
    1970                1975                1980

Asp Asn Ile Thr Ile Leu Lys Thr Tyr Val Cys Leu Gly Ser Lys Leu
1985                1990                1995                2000

Lys Gly Ser Glu Val Tyr Leu Ile Leu Thr Ile Gly Pro Ala Asn Ile
                2005                2010                2015

Leu Pro Val Phe Asp Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
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Lys Gly Ile Lys Thr Ser Leu Ser Lys Leu Lys Ser Val Val Asn Gly
2065 2070 2075 2080

Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
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Lys Leu Ile Asn His Lys His Met Asn Ile Leu Lys Trp Leu Asp His
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Val Leu Asn Phe Arg Ser Ala Glu Leu Asn Tyr Asn His Leu Tyr Met
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Ile Glu Ser Thr Tyr Pro Tyr Leu Ser Glu Leu Leu Asn Ser Leu Thr
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Ser Tyr Leu Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35                  40                  45

Ile Ser Arg Gln Ser Pro Leu Leu Glu His Met Asn Leu Lys Lys Leu
    50                  55                  60

Thr Ile Thr Gln Ser Leu Ile Ser Arg Tyr His Lys Gly Glu Leu Lys
65                  70                  75                  80

Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
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Met Ser Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
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Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
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Asn Lys Leu Gly Leu Lys Glu Lys Asp Arg Val Lys Pro Asn Asn Asn
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Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Ser
                165                 170                 175

His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
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Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
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Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
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Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
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Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
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Ser Tyr Leu Lys Gly Val Ile Ser Phe Ser Glu Cys Asn Ala Leu Gly
            20                  25                  30

Ser Tyr Leu Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
        35                  40                  45

Ile Ser Arg Gln Ser Pro Leu Leu Glu His Met Asn Leu Lys Lys Leu
    50                  55                  60

Thr Ile Thr Gln Ser Leu Ile Ser Arg Tyr His Lys Gly Glu Leu Lys
65                  70                  75                  80

Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
                85                  90                  95

Met Ser Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
            100                 105                 110

Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
        115                 120                 125

Asn Lys Leu Gly Leu Lys Glu Lys Asp Arg Val Lys Pro Asn Asn Asn
    130                 135                 140

Ser Gly Asp Glu Asn Ser Val Leu Thr Thr Ile Ile Lys Asp Asp Ile
145                 150                 155                 160

Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Ser
                165                 170                 175

His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190
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Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205

Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220

Glu Val Lys Ser His Gly Phe Ile Leu Ile Asp Asn Gln Thr Leu Ser
225                 230                 235                 240

Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255

Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270

Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285

Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300

Phe Asn Asn Val Val Leu Ser Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320

Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
                325                 330                 335

Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
            340                 345                 350

Lys Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
        355                 360                 365

Ile Lys Ala Gln Lys Asp Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380

Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
385                 390                 395                 400

Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
                405                 410                 415

Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
            420                 425                 430

Met Val Asp Glu Arg Gln Ala Met Asp Ser Val Arg Ile Asn Cys Asn
        435                 440                 445
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Glu Thr Lys Phe Tyr Leu Leu Ser Ser Leu Ser Thr Leu Arg Gly Ala
    450                 455                 460

Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Thr Tyr Asn Arg Trp
465                 470                 475                 480

Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Asn Tyr
                485                 490                 495

Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Ile Thr Glu Asn Asp
            500                 505                 510

Leu Ile Ile Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe His Leu Pro
        515                 520                 525

Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540

Pro Lys Asp Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560

His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575

Asp Arg Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590

Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605

Asn Ser Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620

Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Ile Gln
625                 630                 635                 640

Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655

Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
            660                 665                 670

Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
        675                 680                 685

Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
    690                 695                 700
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Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705                 710                 715                 720

Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
                725                 730                 735

Ile Pro Leu Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Phe
            740                 745                 750

Ile Lys Asp His Val Val Asn Leu Asn Glu Val Asp Glu Gln Ser Gly
        755                 760                 765

Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
    770                 775                 780

Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785                 790                 795                 800

Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
                805                 810                 815

Ile Ser Lys Pro Val Arg Leu Ile Glu Gly Gln Thr His Ala Gln Ala
            820                 825                 830

Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
        835                 840                 845

Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
    850                 855                 860

Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865                 870                 875                 880

Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
                885                 890                 895

Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
            900                 905                 910

Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
        915                 920                 925

Arg Asn Ile Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Arg Asn His
    930                 935                 940

Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945                 950                 955                 960
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His Leu Lys Thr Phe Phe Asn Leu Asp Ser Ile Asp Met Ala Leu Ser
                965                 970                 975

Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
            980                 985                 990

Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
        995                1000                1005

Ile Val His Ser Val Phe Val Leu Ser Tyr Tyr Thr Gly His Asp Leu
   1010                1015                1020

Gln Asp Lys Leu Gln Asp Leu Pro Asp Asp Arg Leu Asn Lys Phe Leu
1025                1030                1035                1040

Thr Cys Val Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
                1045                1050                1055

Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
            1060                1065                1070

Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Ile Ala
        1075                1080                1085

Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
   1090                1095                1100

Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
1105                1110                1115                1120

Gly Leu Arg Val Val Tyr Glu Ser Leu Pro Phe Tyr Lys Ala Glu Lys
                1125                1130                1135

Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
            1140                1145                1150

Lys Thr Ser Ala Ile Asp Thr Thr Asp Ile Asn Arg Ala Thr Asp Met
        1155                1160                1165

Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
   1170                1175                1180

Asn Lys Asp Lys Arg Glu Leu Leu Ser Leu Glu Asn Leu Ser Ile Thr
1185                1190                1195                1200

Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
                1205                1210                1215
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Val Gly Val Thr Ser Pro Ser Ile Met Phe Thr Met Asn Ile Lys Tyr
          1220                1225                1230

Thr Thr Ser Thr Ile Ala Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
      1235                1240                1245

Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly
  1250                1255                1260

Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
1265                1270                1275                1280

Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
                1285                1290                1295

Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
          1300                1305                1310

Ser Thr Gly Thr Leu Gly Leu Ser Tyr Glu Lys Ala Lys Lys Leu Phe
      1315                1320                1325

Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
  1330                1335                1340

Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
1345                1350                1355                1360

Tyr His Phe Asp Thr Ser Pro Ile Asn His Val Leu Thr Glu Lys Tyr
                1365                1370                1375

Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
          1380                1385                1390

Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Ile Cys Pro Asn
      1395                1400                1405

Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
  1410                1415                1420

Pro Ile Phe Thr Gly Asp Val Asp Ile Ile Lys Leu Lys Gln Val Ile
1425                1430                1435                1440

Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
                1445                1450                1455

Val Glu Leu Phe Leu Ser Asn Lys Ala Leu Lys Ser Gly Ser His Ile
          1460                1465                1470
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Asn Ser Asn Leu Ile Leu Val His Lys Met Ser Asp Tyr Phe His Asn
      1475                1480                1485

Ala Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
   1490                1495                1500

Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
1505                1510                1515                1520

Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Asn Val Phe Phe Asn
                1525                1530                1535

Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
            1540                1545                1550

Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
      1555                1560                1565

Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
   1570                1575                1580

Gln Lys Val Ile Lys Tyr Ile Val Asn Gln Asp Thr Ser Leu Arg Arg
1585                1590                1595                1600

Ile Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asn
                1605                1610                1615

Asn Ala Lys Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
            1620                1625                1630

Pro Thr His Met Lys Ala Ile Leu Ser Tyr Ile Asp Leu Val Arg Met
      1635                1640                1645

Gly Leu Ile Asn Val Asp Lys Leu Thr Ile Lys Asn Lys Asn Lys Phe
   1650                1655                1660

Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Ser Tyr Asn Phe
1665                1670                1675                1680

Ser Asp Asn Thr His Leu Leu Thr Lys Gln Ile Arg Ile Ala Asn Ser
                1685                1690                1695

Glu Leu Glu Asp Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
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Leu Glu Asn Met Ser Leu Ile Pro Val Lys Ser Asn Asn Ser Asn Lys
      1715                1720                1725
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Pro Lys Phe Cys Ile Ser Gly Asn Thr Glu Ser Met Met Met Ser Thr
  1730                1735                1740

Phe Ser Ser Lys Met His Ile Lys Ser Ser Thr Val Thr Thr Arg Phe
1745                1750                1755                1760

Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Ile Val Val Ile
                1765                1770                1775

Asp Lys Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
            1780                1785                1790

Tyr Thr Thr Thr Ser His Gln Thr Ser Leu Val Arg Asn Ser Ala Ser
        1795                1800                1805

Leu Tyr Cys Met Leu Pro Trp His His Val Asn Arg Phe Asn Phe Val
  1810                1815                1820

Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825                1830                1835                1840

Leu Lys Ile Lys Asp Pro Ser Cys Ile Ala Phe Ile Gly Glu Gly Ala
                1845                1850                1855

Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
            1860                1865                1870

Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
        1875                1880                1885

Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
  1890                1895                1900

Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
1905                1910                1915                1920

Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Ile Phe Val Cys Asp
                1925                1930                1935

Ala Glu Leu Pro Val Thr Ala Asn Trp Ser Lys Ile Ile Ile Glu Trp
            1940                1945                1950

Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Arg Cys
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Ile Leu Ile Ala Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
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Lys Gly Ser Glu Val Tyr Leu Ile Leu Thr Ile Gly Pro Ala Asn Ile
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Leu Pro Val Phe Asp Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
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Thr Lys Asn Phe Ile Met Pro Lys Lys Thr Asp Lys Glu Ser Ile Asp
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Lys Gly Ile Lys Thr Ser Leu Ser Lys Leu Lys Ser Val Val Asn Gly
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Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
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Lys Leu Ile Asn His Lys His Met Asn Ile Leu Lys Trp Leu Asp His
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SUBSTITUTE SHEET (RULE 26)

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Ser Tyr Leu Phe Asn Gly Pro Tyr Leu Lys Asn Asp Tyr Thr Asn Leu
35 40 45

Ile Ser Arg Gln Ser Pro Leu Leu Glu His Met Asn Leu Lys Lys Leu
50 55 60

Thr Ile Thr Gln Ser Leu Ile Ser Arg Tyr His Lys Gly Glu Leu Lys
65 70 75 80

Leu Glu Glu Pro Thr Tyr Phe Gln Ser Leu Leu Met Thr Tyr Lys Ser
85 90 95

Met Ser Ser Ser Glu Gln Ile Ala Thr Thr Asn Leu Leu Lys Lys Ile
100 105 110

Ile Arg Arg Ala Ile Glu Ile Ser Asp Val Lys Val Tyr Ala Ile Leu
115 120 125

Asn Lys Leu Gly Leu Lys Glu Lys Asp Arg Val Lys Pro Asn Asn Asn
130 135 140

Ser Gly Asp Glu Asn Ser Val Leu Thr Thr Ile Ile Lys Asp Asp Ile
145 150 155 160

Leu Ser Ala Val Glu Asn Asn Gln Ser Tyr Thr Asn Ser Asp Lys Ser

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                165                 170                 175

His Ser Val Asn Gln Asn Ile Thr Ile Lys Thr Thr Leu Leu Lys Lys
            180                 185                 190

Leu Met Cys Ser Met Gln His Pro Pro Ser Trp Leu Ile His Trp Phe
        195                 200                 205

Asn Leu Tyr Thr Lys Leu Asn Asn Ile Leu Thr Gln Tyr Arg Ser Asn
    210                 215                 220

Glu Val Lys Ser His Gly Phe Ile Leu Ile Asp Asn Gln Thr Leu Ser
225                 230                 235                 240

Gly Phe Gln Phe Ile Leu Asn Gln Tyr Gly Cys Ile Val Tyr His Lys
                245                 250                 255

Gly Leu Lys Lys Ile Thr Thr Thr Thr Tyr Asn Gln Phe Leu Thr Trp
            260                 265                 270

Lys Asp Ile Ser Leu Ser Arg Leu Asn Val Cys Leu Ile Thr Trp Ile
        275                 280                 285

Ser Asn Cys Leu Asn Thr Leu Asn Lys Ser Leu Gly Leu Arg Cys Gly
    290                 295                 300

Phe Asn Asn Val Val Leu Ser Gln Leu Phe Leu Tyr Gly Asp Cys Ile
305                 310                 315                 320

Leu Lys Leu Phe His Asn Glu Gly Phe Tyr Ile Ile Lys Glu Val Glu
                325                 330                 335

Gly Phe Ile Met Ser Leu Ile Leu Asn Ile Thr Glu Glu Asp Gln Phe
            340                 345                 350

Arg Lys Arg Phe Tyr Asn Ser Met Leu Asn Asn Ile Thr Asp Ala Ala
        355                 360                 365

Ile Lys Ala Gln Lys Asp Leu Leu Ser Arg Val Cys His Thr Leu Leu
    370                 375                 380

Asp Lys Thr Val Ser Asp Asn Ile Ile Asn Gly Lys Trp Ile Ile Leu
385                 390                 395                 400

Leu Ser Lys Phe Leu Lys Leu Ile Lys Leu Ala Gly Asp Asn Asn Leu
                405                 410                 415

Asn Asn Leu Ser Glu Leu Tyr Phe Leu Phe Arg Ile Phe Gly His Pro
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          420                 425                 430

Met Val Asp Glu Arg Gln Ala Met Asp Ser Val Arg Ile Asn Cys Asn
        435                 440                 445

Glu Thr Lys Phe Tyr Leu Leu Ser Ser Leu Ser Thr Leu Arg Gly Ala
    450                 455                 460

Phe Ile Tyr Arg Ile Ile Lys Gly Phe Val Asn Thr Tyr Asn Arg Trp
465                 470                 475                 480

Pro Thr Leu Arg Asn Ala Ile Val Leu Pro Leu Arg Trp Leu Asn Tyr
                485                 490                 495

Tyr Lys Leu Asn Thr Tyr Pro Ser Leu Leu Glu Ile Thr Glu Asn Asp
            500                 505                 510

Leu Ile Ile Leu Ser Gly Leu Arg Phe Tyr Arg Glu Phe His Leu Pro
        515                 520                 525

Lys Lys Val Asp Leu Glu Met Ile Ile Asn Asp Lys Ala Ile Ser Pro
    530                 535                 540

Pro Lys Asp Leu Ile Trp Thr Ser Phe Pro Arg Asn Tyr Met Pro Ser
545                 550                 555                 560

His Ile Gln Asn Tyr Ile Glu His Glu Lys Leu Lys Phe Ser Glu Ser
                565                 570                 575

Asp Arg Ser Arg Arg Val Leu Glu Tyr Tyr Leu Arg Asp Asn Lys Phe
            580                 585                 590

Asn Glu Cys Asp Leu Tyr Asn Cys Val Val Asn Gln Ser Tyr Leu Asn
        595                 600                 605

Asn Ser Asn His Val Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser
    610                 615                 620

Val Gly Arg Met Phe Ala Met Gln Pro Gly Met Phe Arg Gln Ile Gln
625                 630                 635                 640

Ile Leu Ala Glu Lys Met Ile Ala Glu Asn Ile Leu Gln Phe Phe Pro
                645                 650                 655

Glu Ser Leu Thr Arg Tyr Gly Asp Leu Glu Leu Gln Lys Ile Leu Glu
            660                 665                 670

Leu Lys Ala Gly Ile Ser Asn Lys Ser Asn Arg Tyr Asn Asp Asn Tyr
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675 680 685

Asn Asn Tyr Ile Ser Lys Cys Ser Ile Ile Thr Asp Leu Ser Lys Phe
690 695 700

Asn Gln Ala Phe Arg Tyr Glu Thr Ser Cys Ile Cys Ser Asp Val Leu
705 710 715 720

Asp Glu Leu His Gly Val Gln Ser Leu Phe Ser Trp Leu His Leu Thr
725 730 735

Ile Pro Leu Val Thr Ile Ile Cys Thr Tyr Arg His Ala Pro Pro Phe
740 745 750

Ile Lys Asp His Val Val Asn Leu Asn Glu Val Asp Glu Gln Ser Gly
755 760 765

Leu Tyr Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu
770 775 780

Trp Thr Ile Glu Ala Ile Ser Leu Leu Asp Leu Ile Ser Leu Lys Gly
785 790 795 800

Lys Phe Ser Ile Thr Ala Leu Ile Asn Gly Asp Asn Gln Ser Ile Asp
805 810 815

Ile Ser Lys Pro Val Arg Leu Ile Glu Gly Gln Thr His Ala Gln Ala
820 825 830

Asp Tyr Leu Leu Ala Leu Asn Ser Leu Lys Leu Leu Tyr Lys Glu Tyr
835 840 845

Ala Gly Ile Gly His Lys Leu Lys Gly Thr Glu Thr Tyr Ile Ser Arg
850 855 860

Asp Met Gln Phe Met Ser Lys Thr Ile Gln His Asn Gly Val Tyr Tyr
865 870 875 880

Pro Ala Ser Ile Lys Lys Val Leu Arg Val Gly Pro Trp Ile Asn Thr
885 890 895

Ile Leu Asp Asp Phe Lys Val Ser Leu Glu Ser Ile Gly Ser Leu Thr
900 905 910

Gln Glu Leu Glu Tyr Arg Gly Glu Ser Leu Leu Cys Ser Leu Ile Phe
915 920 925

Arg Asn Ile Trp Leu Tyr Asn Gln Ile Ala Leu Gln Leu Arg Asn His

930 935 940

Ala Leu Cys Asn Asn Lys Leu Tyr Leu Asp Ile Leu Lys Val Leu Lys
945 950 955 960

His Leu Lys Thr Phe Phe Asn Leu Asp Ser Ile Asp Met Ala Leu Ser
965 970 975

Leu Tyr Met Asn Leu Pro Met Leu Phe Gly Gly Gly Asp Pro Asn Leu
980 985 990

Leu Tyr Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala
995 1000 1005

Ile Val His Ser Val Phe Val Leu Ser Tyr Tyr Thr Gly His Asp Leu
1010 1015 1020

Gln Asp Lys Leu Gln Asp Leu Pro Asp Asp Arg Leu Asn Lys Phe Leu
1025 1030 1035 1040

Thr Cys Val Ile Thr Phe Asp Lys Asn Pro Asn Ala Glu Phe Val Thr
1045 1050 1055

Leu Met Arg Asp Pro Gln Ala Leu Gly Ser Glu Arg Gln Ala Lys Ile
1060 1065 1070

Thr Ser Glu Ile Asn Arg Leu Ala Val Thr Glu Val Leu Ser Ile Ala
1075 1080 1085

Pro Asn Lys Ile Phe Ser Lys Ser Ala Gln His Tyr Thr Thr Thr Glu
1090 1095 1100

Ile Asp Leu Asn Asp Ile Met Gln Asn Ile Glu Pro Thr Tyr Pro His
1105 1110 1115 1120

Gly Leu Arg Val Val Tyr Glu Ser Leu Pro Phe Tyr Lys Ala Glu Lys
1125 1130 1135

Ile Val Asn Leu Ile Ser Gly Thr Lys Ser Ile Thr Asn Ile Leu Glu
1140 1145 1150

Lys Thr Ser Ala Ile Asp Thr Thr Asp Ile Asn Arg Ala Thr Asp Met
1155 1160 1165

Met Arg Lys Asn Ile Thr Leu Leu Ile Arg Ile Leu Pro Leu Asp Cys
1170 1175 1180

Asn Lys Asp Lys Arg Glu Leu Leu Ser Leu Glu Asn Leu Ser Ile Thr

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1185                1190                1195                1200

Glu Leu Ser Lys Tyr Val Arg Glu Arg Ser Trp Ser Leu Ser Asn Ile
                1205                1210                1215

Val Gly Val Thr Ser Pro Ser Ile Met Phe Thr Met Asp Ile Lys Tyr
            1220                1225                1230

Thr Thr Ser Thr Ile Ala Ser Gly Ile Ile Ile Glu Lys Tyr Asn Val
        1235                1240                1245

Asn Ser Leu Thr Arg Gly Glu Arg Gly Pro Thr Lys Pro Trp Val Gly
    1250                1255                1260

Ser Ser Thr Gln Glu Lys Lys Thr Met Pro Val Tyr Asn Arg Gln Val
1265                1270                1275                1280

Leu Thr Lys Lys Gln Arg Asp Gln Ile Asp Leu Leu Ala Lys Leu Asp
                1285                1290                1295

Trp Val Tyr Ala Ser Ile Asp Asn Lys Asp Glu Phe Met Glu Glu Leu
            1300                1305                1310

Ser Thr Gly Thr Leu Gly Leu Ser Tyr Glu Lys Ala Lys Lys Leu Phe
        1315                1320                1325

Pro Gln Tyr Leu Ser Val Asn Tyr Leu His Arg Leu Thr Val Ser Ser
    1330                1335                1340

Arg Pro Cys Glu Phe Pro Ala Ser Ile Pro Ala Tyr Arg Thr Thr Asn
1345                1350                1355                1360

Tyr His Phe Asp Thr Ser Pro Ile Asn His Val Leu Thr Glu Lys Tyr
                1365                1370                1375

Gly Asp Glu Asp Ile Asp Ile Val Phe Gln Asn Cys Ile Ser Phe Gly
            1380                1385                1390

Leu Ser Leu Met Ser Val Val Glu Gln Phe Thr Asn Ile Cys Pro Asn
        1395                1400                1405

Arg Ile Ile Leu Ile Pro Lys Leu Asn Glu Ile His Leu Met Lys Pro
    1410                1415                1420

Pro Ile Phe Thr Gly Asp Val Asp Ile Ile Lys Leu Lys Gln Val Ile
1425                1430                1435                1440

Gln Lys Gln His Met Phe Leu Pro Asp Lys Ile Ser Leu Thr Gln Tyr
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                1445                1450                1455

Val Glu Leu Phe Leu Ser Asn Lys Ala Leu Lys Ser Gly Ser His Ile
            1460                1465                1470

Asn Ser Asn Leu Ile Leu Val His Lys Met Ser Asp Tyr Phe His Asn
        1475                1480                1485

Ala Tyr Ile Leu Ser Thr Asn Leu Ala Gly His Trp Ile Leu Ile Ile
    1490                1495                1500

Gln Leu Met Lys Asp Ser Lys Gly Ile Phe Glu Lys Asp Trp Gly Glu
1505                1510                1515                1520

Gly Tyr Ile Thr Asp His Met Phe Ile Asn Leu Asn Val Phe Phe Asn
                1525                1530                1535

Ala Tyr Lys Thr Tyr Leu Leu Cys Phe His Lys Gly Tyr Gly Lys Ala
            1540                1545                1550

Lys Leu Glu Cys Asp Met Asn Thr Ser Asp Leu Leu Cys Val Leu Glu
        1555                1560                1565

Leu Ile Asp Ser Ser Tyr Trp Lys Ser Met Ser Lys Val Phe Leu Glu
    1570                1575                1580

Gln Lys Val Ile Lys Tyr Ile Val Asn Gln Asp Thr Ser Leu Arg Arg
1585                1590                1595                1600

Ile Lys Gly Cys His Ser Phe Lys Leu Trp Phe Leu Lys Arg Leu Asp
                1605                1610                1615

Asn Ala Lys Phe Thr Val Cys Pro Trp Val Val Asn Ile Asp Tyr His
            1620                1625                1630

Pro Thr His Met Lys Ala Ile Leu Ser Tyr Ile Asp Leu Val Arg Met
        1635                1640                1645

Gly Leu Ile Asn Val Asp Lys Leu Thr Ile Lys Asn Lys Asn Lys Phe
    1650                1655                1660

Asn Asp Glu Phe Tyr Thr Ser Asn Leu Phe Tyr Ile Ser Tyr Asn Phe
1665                1670                1675                1680

Ser Asp Asn Thr His Leu Leu Thr Lys Gln Ile Arg Ile Ala Asn Ser
                1685                1690                1695

Glu Leu Glu Asp Asn Tyr Asn Lys Leu Tyr His Pro Thr Pro Glu Thr
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          1700                1705                1710

Leu Glu Asn Met Ser Leu Ile Pro Val Lys Ser Asn Asn Ser Asn Lys
      1715                1720                1725

Pro Lys Phe Cys Ile Ser Gly Asn Thr Glu Ser Met Met Met Ser Thr
   1730                1735                1740

Phe Ser Ser Lys Met His Ile Lys Ser Ser Thr Val Thr Thr Arg Phe
1745                1750                1755                1760

Asn Tyr Ser Lys Gln Asp Leu Tyr Asn Leu Phe Pro Ile Val Val Ile
                1765                1770                1775

Asp Lys Ile Ile Asp His Ser Gly Asn Thr Ala Lys Ser Asn Gln Leu
          1780                1785                1790

Tyr Thr Thr Thr Ser His Gln Thr Ser Leu Val Arg Asn Ser Ala Ser
      1795                1800                1805

Leu Tyr Cys Met Leu Pro Trp His His Val Asn Arg Phe Asn Phe Val
   1810                1815                1820

Phe Ser Ser Thr Gly Cys Lys Ile Ser Ile Glu Tyr Ile Leu Lys Asp
1825                1830                1835                1840

Leu Lys Ile Lys Asp Pro Ser Cys Ile Ala Phe Ile Gly Glu Gly Ala
                1845                1850                1855

Gly Asn Leu Leu Leu Arg Thr Val Val Glu Leu His Pro Asp Ile Arg
          1860                1865                1870

Tyr Ile Tyr Arg Ser Leu Lys Asp Cys Asn Asp His Ser Leu Pro Ile
      1875                1880                1885

Glu Phe Leu Arg Leu Tyr Asn Gly His Ile Asn Ile Asp Tyr Gly Glu
   1890                1895                1900

Asn Leu Thr Ile Pro Ala Thr Asp Ala Thr Asn Asn Ile His Trp Ser
1905                1910                1915                1920

Tyr Leu His Ile Lys Phe Ala Glu Pro Ile Ser Ile Phe Val Cys Asp
                1925                1930                1935

Ala Glu Leu Pro Val Thr Ala Asn Trp Ser Lys Ile Ile Ile Glu Trp
          1940                1945                1950

Ser Lys His Val Arg Lys Cys Lys Tyr Cys Ser Ser Val Asn Arg Cys
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      1955                1960                1965

Ile Leu Ile Ala Lys Tyr His Ala Gln Asp Asp Ile Asp Phe Lys Leu
   1970                1975                1980

Asp Asn Ile Thr Ile Leu Lys Thr Tyr Val Cys Leu Gly Ser Lys Leu
1985                1990                1995                2000

Lys Gly Ser Glu Val Tyr Leu Ile Leu Thr Ile Gly Pro Ala Asn Ile
                2005                2010                2015

Leu Pro Val Phe Asp Val Val Gln Asn Ala Lys Leu Ile Leu Ser Arg
            2020                2025                2030

Thr Lys Asn Phe Ile Met Pro Lys Lys Thr Asp Lys Glu Ser Ile Asp
        2035                2040                2045

Ala Val Ile Lys Ser Leu Ile Pro Phe Leu Cys Tyr Pro Ile Thr Lys
    2050                2055                2060

Lys Gly Ile Lys Thr Ser Leu Ser Lys Leu Lys Ser Val Val Asn Gly
2065                2070                2075                2080

Asp Ile Leu Ser Tyr Ser Ile Ala Gly Arg Asn Glu Val Phe Ser Asn
                2085                2090                2095

Lys Leu Ile Asn His Lys His Met Asn Ile Leu Lys Trp Leu Asp His
            2100                2105                2110

Val Leu Asn Phe Arg Ser Ala Glu Leu Asn Tyr Asn His Leu Tyr Met
        2115                2120                2125

Ile Glu Ser Thr Tyr Pro Tyr Leu Ser Glu Leu Leu Asn Ser Leu Thr
    2130                2135                2140

Thr Asn Glu Leu Lys Lys Leu Ile Lys Ile Thr Gly Ser Val Leu Tyr
2145                2150                2155                2160

Asn Leu Pro Asn Glu Gln
                2165
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